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EWING'S SARCOMA*

A Study of Fifty Cases Treated at the Massachusetts General Hospital, 1930–1952 Inclusive

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BOSTON

EWING'S sarcoma was first described by James Ewing in 1921.[1,2] Since then a voluminous literature regarding this interesting disease has appeared. The pathogenesis, histology, clinical features, and roentgenographic appearance have been extensively studied.[3-9] The purpose of the present investigation is to analyze a group of patients treated at the Massachusetts General Hospital from 1930 through 1952 inclusive.

Fifty cases of histologically proved Ewing sarcoma form this group, 36 patients being treated by external radiation alone, 10 by radical surgery, and 4 by surgery followed by x-ray therapy. Of the 36 given radiation alone, 22 at the time of admission showed a single lesion without evidence of distant metastases; in 14 metastases were already apparent, and treatment was directed toward palliation only. No metastases were recognized in the 14 treated surgically.

Tables 1 and 2 summarize the cases and the results of treatment. Males were slightly predominant in the group — 27 were males, and 23 females.

Table 3 shows the age distribution of the patients at the time of admission to the hospital. The youngest was three and a half years, and the oldest forty-three years of age. Twenty-nine were in the second decade of life; 33, or 66 per cent, were under twenty years of age, and only 3 were over forty.

The known duration of symptoms before medical advice was sought was less than three months in 23, four to six months in 11, seven to twelve months in 9, thirteen to eighteen months in 2, nineteen to twenty-four months in 3, and twenty-five to thirty-six months in 2 cases.

The clinical manifestations of the disease varied. In 24 cases pain was the first symptom; in 11 patients there was swelling of the affected part; 13 had both pain and swelling; in 3 a limp was observed; in 1 there was paralysis of an extremity; and 1 had fever and cough.

TABLE 1. *Patients with Ewing's Sarcoma Treated at the Massachusetts General Hospital, 1930–1952.*

Case No.	Sex	Age	Symptoms	Duration	Primary Location	Operation	Result	Period of Survival	Remarks
		yr.							
Group A (treatment with radical surgery):									
1	M	15	Swelling	3 yr.	Radius	Amputation	Dead with disease	40 mo.	
2	M	16	Pain and swelling	3 wk.	Tibia	Low-thigh amputation	Dead with disease	10 mo.	
3	F	23	Pain and swelling	6 mo.	Tarsal	Amputation	Dead with disease	5 mo.	
4	M	20	Pain and swelling	6 wk.	Fibula	Gritti-Stokes amputation	Dead with disease	19 mo.	
5	M	30	Pain	2 yr.	Tibia	Low-thigh amputation	Living without disease	6 yr.	Lost after 6 yr.
6	M	16	Pain and swelling	3 mo.	Fibula	Low-thigh amputation	Dead with disease	4 mo.	
7	F	14	Swelling	2 yr.	Mandible	Resection, rt. lower jaw	Dead with disease	30 mo.	
8	F	34	Pain	1 yr.	Tibia	Low-thigh amputation	Dead with disease	48 mo.	
9	F	13	Swelling	18 mo.	Fibula	Low-thigh amputation	Dead with disease	28 mo.	
10	M	15	Swelling	3 mo.	Fibula	Low-thigh amputation	Dead with disease	6 mo.	
Group B (radical surgery with postoperative irradiation):									
11	M	19	Pain	3 mo.	Sacrum	Excision + 5000 r	Dead with disease	3 mo.	
12	M	20	Pain and swelling	3 mo.	Fibula	Resection + x-ray	Dead with disease	2 mo.	Tumor dose unknown
13	M	18	Pain	4 mo.	Rib	Rib resection + 5000 r	Dead with disease	5 mo.	Irradiation to lt. side of chest
14	F	40	Pain and swelling	4 mo.	Rib	Rib resection + 4000 r	Dead with disease	6 mo.	Irradiation to lt. side of chest

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The location of the primary lesion was in accord with the generally accepted concept that the majority of Ewing tumors originate below the waist line.[4, 7] Thirty-four of this group (68 per cent) were so located (Table 4).

The results of treatment were analyzed (Tables 1 and 2). Of the surgically treated patients, only 1 lived more than five years. Although the final outcome is unknown, this patient was alive and without apparent disease six years after operation. Nine patients in this group died of their disease; 4 within a year, and 1 nineteen months, 2 between two and three years, and 2 between three and four years after operation. In this group the primary tumor was located, with 1 exception, in an extremity. The tibia was the site in 3 cases, the fibula in 4, the radius in 1, a tarsal bone in 1, and the mandible in another.

TABLE 2. *Patients Given X-ray Therapy Alone.*

Case No.	Sex	Age	Symptoms	Duration	Primary Location	Year Treated	Dosage	Result	Period of Survival	Remarks
		yr.								
Group C (radical x-ray treatment):										
15	F	11	Swelling	8 mo.	Femur	1946	6000 r	Dead from metastases	12 mo.	Primary controlled
16	F	18	Pain	1 mo.	Femur	1952	4000 r	Living without disease	6 mo.	Primary controlled
17	F	29	Swelling	4 mo.	Mandible	1950	3600 r	Living without disease	2 yr.	Primary controlled
18	F	7	Limp	3 wk.	Femur	1942	5000 r	Dead from metastases	5 mo.	Primary controlled
			Pain and swelling	2 wk.						
19	M	26	Pain and swelling	4 mo.	Rib	1947	5000 r	Death from metastases	12 mo.	Primary controlled
20	F	12	Pain	2 mo.	Pubis	1943	3000 r	Living without disease	9 yr.	Primary controlled
21	F	20	Pain and swelling	8 mo.	Fibula	1941	4500 r	Living without disease	12 yr.	Primary controlled
22	M	14	Pain and swelling	2 mo.	Rib	1950	4000 r	Dead from metastases	11 mo.	Primary controlled; pulmonary metastases disappeared after 1000 r given to chest.
23	M	10	Swelling	2 mo.	Ilium	1942	4000 r	Dead from metastases	19 mo.	Primary controlled
24	F	18	Swelling	2 mo.	Femur	1938	14 r (? tumor dose)	Dead with disease	7 mo.	Primary uncontrolled
25	F	21	Swelling	3 mo.	Clavicle	1946	3000 r*	Living without disease	6½ yr.	Primary controlled; specimen negative for tumor.
26	M	8	Fever and cough	1 mo.	Rib	1939	3500 r	Living without disease	13 yr.	Primary controlled
27	M	12	Pain	3 yr.	Pubis	1945	4000 r	Dead from metastases	6½ yr.	Primary controlled; multiple x-ray therapy and Coley's toxin.
28	M	12	Pain	3 mo.	Ilium	1944	3000 r	Dead with disease	3 wk.	
29	F	13	Limp	3 mo.	Ilium	1939	3000 r	Dead with disease	9 mo.	Primary uncontrolled
30	F	17	Pain	6 mo.	Pubis	1945	5000 r	Dead with disease	10 mo.	
31	M	25	Pain	5 mo.	Pelvis	1938	3000 r	Dead with disease	7 mo.	Primary uncontrolled
32	F	10	Pain	8 mo.	Rib	1948	5000 r	Living with disease	4 yr.	Primary controlled; comfortable with repeated palliative radiation.
33	M	28	Pain	6 mo.	Femur	1944	5000 r	Dead from metastases	10 mo.	Primary controlled
34	M	12	Pain	3 mo.	Sacrum	1940	2000 r	Dead with disease	2 mo.	
35	M	16	Pain	2 mo.	Femur	1944	4000 r	Dead with disease	14 mo.	Primary uncontrolled
36	F	16	Pain	1 yr.	Fibula	1944	5000 r	Dead from metastases	6 mo.	Primary controlled
Group D (palliative x-ray treatment):										
37	M	17	Swelling	1 mo.	Pubis	1936	2000 r	Dead from metastases	42 mo.	Primary controlled; patient comfortable with repeated doses of 1000 r.
38	F	3½	Pain, swelling and limp	3 mo.	Femur	1934	600 r	Dead with disease	10 mo.	Primary uncontrolled
39	M	14	Pain	1 yr.	Femur	1942	4000 r	Dead from metastases	9 mo.	Primary controlled
40	F	5	Pain and swelling	1 yr.	Humerus	1931	1000 r	Dead with disease	3 mo.	Primary uncontrolled
41	M	43	Pain	6 mo.	Rib	1931	(Dose unknown)	Dead with disease	6 mo.	Primary uncontrolled
42	F	10	Pain	6 mo.	Spine	1936	(Dose unknown)	Dead with disease	12 mo.	
43	F	10	Pain and paralysis	18 mo.	Sacrum	1945	900 r	Dead with disease	3 mo.	Primary uncontrolled
44	M	23	Pain	2 mo.	Ilium	1944	1200 r	Dead with disease	2 mo.	Primary uncontrolled
45	F	27	Pain	1 yr.	Rib	1947	2000 r	Dead with disease	10 mo.	Primary uncontrolled
46	M	17	Pain	9 mo.	Tibia	1948	2000 r	Dead with disease	4 mo.	
47	F	14	Pain	2 mo.	Pubis	1932	1000 r	Dead with disease	7 mo.	
48	M	40	Pain	3 yr.	Spine†	1932	1000 r	Dead from metastases	7 yr.	Primary controlled
49	M	18	Swelling	3 wk.	Widespread metastases	1948	1200 r	Dead with disease	6 mo.	
50	M	33	Pain and swelling	2 yr.	Femur	1948	1000 r	Dead with disease	2 mo.	Primary uncontrolled

*Resection 2 mo. later.
†Fifth lumbar segment.

Of the 4 patients in whom operation was followed by radiation, 2, each with a lesion of a rib, died within six months; 1 died with a tumor in a fibula within three months, and 1 with a lesion of the sacrum was lost to follow-up study after three months but at this time was known to have pulmonary metastases.

Of 22 patients who received external radiation aimed at cure of the disease, 4 have survived without disease for six and a half, nine, twelve and thirteen years. Three others are living, one for four years but with disease, and 2 without disease for two years and six months respectively. Fifteen patients died of their disease. One, in whom pulmonary metastases developed sixteen months after treatment, lived for five and a quarter years before he succumbed. Twelve patients died within a year of treatment; 1 survived for fourteen months and another for nineteen months after irradiation.

Of those given palliative irradiation, 1 lived for seven years after the initial treatment, eventually dying of widespread metastases. On admission pulmonary metastases had already developed; these, as well as the primary tumor in the spine, were treated palliatively with small amounts of radiation (1000 r). Twelve of the group died with disease within a year; 1 died with disease forty-two months after the initial treatment.

The effects of radiation on the primary lesion were also studied. Twenty-seven patients were completely relieved of pain shortly after treatment was instituted. In most of the cases in which treatment was given for palliative purposes, it was successful, and the patient enjoyed considerable subjective relief.

Serial roentgenograms were available in 16 of the 22 patients treated with radiation aimed at cure. Fourteen showed definite radiographic improvement, consisting of the disappearance of the soft-tissue mass and reossification of the destroyed bone. In 2 cases no change in the appearance of the bone was apparent nineteen and fourteen months after treatment.

Clinically, 15 of the 22 irradiated tumors gave no evidence of local recurrence; in 4, the tumor was not controlled. The response to radiation was undetermined in 3 cases. Three patients with uncontrolled tumors received a tumor dose of 3000 to 4000 r and died of disease within seven, nine and 14 months; in the fourth, the exact x-ray dosage given is unrecorded; the patient died with disease seven months after the initial therapy.

The maximum tumor dose administered was 6000 r. Seven patients received a dose between 5000 and 6000 r (Table 5). It is interesting that a dosage as small as 1000 r was sufficient to control the local lesion in 1 case (Case 48). Of 4 patients who received no more than 2000 r to the primary lesion, 1 (Case 37) was satisfactorily controlled, 1 (Case 45) was not controlled, and in 2 the result was undetermined but considered unsatisfactory. One patient (Case 25) whose tumor received 3000 r was operated upon two months later; multiple histologic sections of the specimen failed to disclose tumor cells although the original biopsy slide has been reviewed repeatedly and the diagnosis of Ewing's tumor confirmed. On the other hand, 1 patient (Case 19), who received approximately 5000 r and had no clinical or radiographic evidence of local recurrence, died of distant metastases twelve months later, and at post-mortem examination the primary lesion still contained a few viable tumor cells surrounded by areas of radiation fibrosis with thromboendarteritis.

Treatment in the majority of cases in this hospital was given with supervoltage x-ray (1200 to 2000 Kv), an estimated daily tumor dose of 150 to

TABLE 3. *Age Distribution.*

Age yr.	No. of Patients
0–9	4
10–19	29
20–29	11
30–39	3
40 and over	3
Total	50

TABLE 4. *Location of Primary Tumor.*

Location	No. of Cases
Pelvis	13
Femur	9
Rib	8
Fibula	7
Tibia	4
Humerus	1
Mandible	2
Spine	2
Tarsal	1
Clavicle	1
Radius	1
Metastases, widespread	1

TABLE 5. *X-ray Dosage and Effect in Cases Irradiated.*

Dosage r	Controlled Tumors	Tumors Not Controlled	Undetermined	Total
600	0	1	0	1
1000	1	4	2	7
2000	1	1	2	4
3000	2	2	1	5
3500	2	0	0	2
4000	5	1	0	6
4500	1	0	0	1
5000	5*	0	1	6
6000	1	0	0	1
Unknown	0	2	1	3

*In 1 of these, microscopical evidence of residual disease was found at post-mortem examination.

200 r being administered. The treatment field included the entire bone in which the primary lesion was located.

The results in patients who survived five years or more are presented in Table 6. The following

This case and the next (Case 26) demonstrate the fact that apparent cures without deformity can be obtained by radiation therapy.

CASE 26. An 8-year-old boy was first seen at the Collis P. Huntington Memorial Hospital in July, 1939. One month

TABLE 6. *Summary of Patients Who Survived for More Than Five Years.*

CASE No.	AGE	SEX	PRIMARY LOCATION	DURATION OF SYMPTOMS	METHOD OF TREATMENT	PERIOD OF SURVIVAL	REMARKS
	yr.			mo.		yr.	
5	30	M	Tibia	24	Amputation	6	No later follow-up report
20	12	F	Pubis	2	Irradiation (3000 r)	9	Patient living without disease
21	20	F	Fibula	8	Irradiation (4500 r)	12	Patient living without disease
25	21	F	Clavicle	3	Irradiation (3000 r); resection 2 mo. later.	6	Patient living without disease
26	8	M	Rib	1	Irradiation (3500 r)	13	Patient living without disease
27	12	M	Pubis	36	Irradiation (4000 r)	6½	Patient died of generalized metastases
48	40	M	Spine (lung)	2	Irradiation (1000 r)	7	Patient died of generalized metastases

brief case reports illustrate certain points in the treatment of Ewing's tumor.

CASE REPORT

CASE 20. In October, 1943, a 12-year-old girl was admitted to the hospital complaining of pain in the region of the vulva that had been present for about 2 months. The pain was most severe when she was sitting down. There was no history of injury, fever, chills or redness. Physical examination was negative except for some tenderness in the left thigh close to the vulva, particularly on pressure over the ischium. Roentgenograms of the chest were normal. The pelvis showed an area of destruction in the left ischium and pubis. Biopsy proved the lesion to be a Ewing tumor. It was decided to give the patient x-ray treatment despite the fact that she had not yet shown signs of puberty. Treatment was given, half with supervoltage and half with 200-Kv x-rays, directed to the left ischium and pubis through anterior and posterior portals, 10 x 10 cm. in size. A total tumor dose of 3000 r was administered at the rate of 300 r (air) per day in 3 weeks' time.

One month after completion of treatment the patient was free of discomfort; in another month, a roentgenogram showed considerable healing of the tumor.

During the subsequent period of observation, 9 years in all, the patient has done well and has developed in normal fashion. Menstruation was established 4 months after completion of x-ray therapy, and has continued normally. She was seen in 1952, 9 years after irradiation, and at that time there was no evidence of local recurrence or of distant metastases. It is a curious and interesting observation that despite irradiation over the pelvis in a child of 12, epiphyseal development was not disturbed, bone growth continued normally, and ovarian function was not interfered with.

CASE 21. A 20-year-old girl was first seen in January, 1941, complaining of painful swelling of the right ankle. Six months previously a roentgenogram had been reported as showing a bone tumor at the lower end of the fibula. Biopsy was performed and the histologic diagnosis was Ewing's tumor. X-ray treatment was instituted. With 1200-Kv x-rays, an estimated tumor dose of 4500 r was given through a field 10 x 20 cm. at the rate of 300 r (air) per day in about 3 weeks' time.

One month after completion of treatment the pain and swelling had disappeared, and the patient was leading a normal, active life. She later married and has remained free of disease for 12 years. Examination at the end of that time showed no abnormalities, with no evidence of tumor either clinically or roentgenologically. A roentgenogram taken 6 months after treatment had revealed complete disappearance of the soft-tissue swelling and partial reconstitution of bone, which has remained essentially unchanged over the ensuing years.

previously he had been struck by an automobile, sustaining bruises about the head and face. A week later a "cold" had developed, and a roentgenogram of the chest showed fluid in the right pleural cavity and a destructive lesion involving the right 9th rib. The lesion was biopsied, and the histologic diagnosis was Ewing's tumor. (This slide has been repeatedly reviewed by different pathologists, and with each re-examination the diagnosis of Ewing's tumor has been considered most likely.)

In July supervoltage radiation was given at the rate of 150 r per day for a total of approximately 3500 r over the involved rib and right side of the chest.

There has been no recurrence of the tumor, and the patient has remained well. He has developed normally, and when last seen in 1952, 13 years after treatment, roentgenologic examination gave no evidence of recurrence. There was slight deformity of the rib at the site of the primary tumor.

CASE 25. In May, 1946, a 21-year-old single woman entered another hospital complaining of a soft, nontender walnut-sized mass over the right clavicle, which had been present for 1 month. There was no history of trauma, and there had been no fever or chills. The mass was biopsied and a histologic diagnosis of Ewing's sarcoma made. The patient received radiotherapy for an approximate dose of 3000 r at the rate of 350 r (air) in 10 days' time.

Two months later she was admitted to the Massachusetts General Hospital, and the right clavicle was resected. Multiple histologic examinations of the specimen through the involved areas disclosed fibrosis and bone resorption but n- tumor tissue. Re-examination by the Pathology Departo ment of the slide of the original biopsy agreed with the diagnosis of Ewing's tumor. The patient has been free of disease for 6½ years since operation.

This case provides histologic evidence of the curability of Ewing's tumor by radiotherapy administered in comparatively small amounts.

CASE 19. A 26-year-old man was admitted to the hospital in August, 1947, complaining of pain and swelling of the left midportion of the chest of 4 months' duration. A roentgenogram of the chest showed the lung fields to be intrinsically clear. There was extensive destruction of the left 7th rib, with an adjacent soft-tissue mass. The mass was biopsied and diagnosed histologically as Ewing's sarcoma. The tumor was treated with external radiation given with supervoltage (1200-Kv) x-rays for an approximate tumor dose of 5000 r at the daily rate of 300 r (air incident) in 4 weeks' time.

One week after completion of radiation therapy a roentgenogram of the chest demonstrated marked regression of the tumor and evidence of new bone formation about the previously destroyed rib.

The patient did well until July, 1948, when he experienced cough and vague fleeting pain in both sides of the chest. A

roentgenogram disclosed metastatic lesions in the right lung and bone destruction in the left 11th rib. The primary lesion, however, showed no recurrence, and reossification of the 7th rib was apparent. Three months after discharge the patient finally succumbed to his disease in another hospital. Postmortem examination revealed extensive metastases to both lungs, hilar lymph nodes, heart, right adrenal gland and right kidney. Histologic sections of the previously irradiated 7th rib showed abundant dense fibrosis, with occasional marked thickening and irregular bone formation. There were a few foci of organizing hemorrhage, and occasional viable tumor cells. There was marked radiation reaction about the blood vessels.

This case illustrates the point that Ewing's tumor occasionally persists after even large doses of radiation.

Discussion

Ewing's sarcoma is a highly, though not uniformly, radiosensitive malignant bone tumor. It differs considerably from other tumors of bone although it may closely resemble osteogenic sarcoma in its radiographic appearance and may resemble osteomyelitis in both its clinical and radiographic aspects. Thirty-three, or 66 per cent, of the 50 patients comprising this series, were under twenty years of age. The malignancy of Ewing's sarcoma appears to vary considerably. Certain patients who when first seen already have metastatic disease may receive only a small amount of radiation and yet have a long-term survival. In the present group of the 22 treated by radiation aimed at cure, 15 were locally controlled, and of these 4 survived for more than five years without disease. One patient is still living four years after the initial treatment but now shows distant metastases although the primary lesion has been clinically controlled (Case 32).

Control of local disease by radiation compares favorably with that by surgical removal and entails no bodily mutilation. If metastases have occurred the salvage is as good and the patient's activity may be maintained at a more normal level. After radical operations only 1 of 10 patients survived for more than five years without disease; 2 lived for more than three years after operation before dying of the disease. None of 4 patients who had radical operations followed by x-ray treatment survived for more than six months. Of 14 patients who showed distant disease when first seen and whose treatment was palliative only, 1 lived for three and a half and 1 for seven years before succumbing to the disease.

In treating any tumor of bone, particularly Ewing's sarcoma, the radiologist should remember that the neoplasm extends longitudinally for a considerable distance beyond the area shown on the roentgenogram.[6] Therefore, the area treated should be large regardless of the apparent size of the tumor; when possible, the entire bone in which the tumor is located should be irradiated. Carefully filtered x-rays of rather high voltage, preferably supervoltage, should be administered through sufficient portals of entry to bring about an adequate tumor dose.

The exact dose required to destroy a Ewing tumor has not been established. In the present group, 1 patient whose primary and secondary lesions were temporarily controlled with only 1000 r survived for seven years of fairly comfortable life. A tissue dose of 3000 r can destroy a tumor (Cases 20 and 25). On the other hand, a dose as high as 5000 r may not completely and microscopically eradicate the disease in an occasional case (Case 19). It is believed, therefore, that a tumor dose of approximately 4000 to 5000 r, fractionated at the rate of 200 to 300 r (air incident) per day, is probably sufficient for primary control of the majority of Ewing's sarcomas.

As in patients with an isolated primary tumor, in those with distant metastases radiation is undoubtedly the treatment of choice. It offers the patient palliation. Discomfort and pain can be relieved, and in many cases life is prolonged — not mere existence but moderately normal and active life. The palliative dose can be rather small. The literature reports, however, a few "hopeless" cases with solitary metastatic lesions in the lungs in which long-term survival was obtained after vigorous radiation therapy.[10] It seems possible that larger dosage should be employed in these "hopeless" cases and that the aim should be "cure" rather than "palliation."

It should be noted that a patient may succumb to the disease although the tumor has been controlled for more than five years (Case 48).

Summary and Conclusions

A group of 50 cases of Ewing's sarcoma treated at the Massachusetts General Hospital is analyzed.

Seven patients survived for more than five years — 6 after radiation therapy, and 1 after radical surgery. Five of these patients were apparently cured; 2 ultimately died of the disease.

External radiation is considered the method of choice in the treatment of this particular type of malignant tumor.

Ewing's tumor of bone is a highly radiosensitive lesion. It has a variable natural history and does not always follow the expected relentless course of a highly malignant neoplasm. If accessible, the local disease can be controlled by surgical means; control by adequate irradiation can be accomplished in a comparably high percentage of cases. Experience suggests that irradiation is the treatment of choice. It does not lessen the chance of survival and does not deprive the patient of a useful or cosmetically desirable part. In a small number of patients (18 per cent of 22 radically irradiated in the present series) apparent cures were obtained. Palliative radiation therapy gives not only relief

of discomfort but also an often unexpectedly long and useful life.

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DIBENZYLINE: RESULTS OF THERAPY IN PATIENTS WITH HYPERTENSION AND A COMPARISON WITH HEXAMETHONIUM, 1-HYDRAZINOPHTHALAZINE AND SEMIPURIFIED EXTRACTS OF VERATRUM*

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ALTHOUGH etiologic factors in hypertensive vascular disease are probably numerous, pharmacologic study indicates that in many cases a common denominator is overactivity of the sympathetic nervous system. Therefore, a drug that will specifically block the transmission of impulses over the sympathetic nervous system should be a valuable therapeutic agent for this disease. Dibenzyline (N-phenoxyisopropyl-N-benzyl-β-chlorethylamine)¶ is a specific, orally active, adrenergic blocking agent that we have used in the treatment of 32 patients under hospital and outpatient conditions. A comparison of the results obtained with this drug and those obtained with hexamethonium, 1-hydrazinophthalazine (Apresoline) and the *Veratrum viride* alkaloids (Veriloid and Anatensol) form the basis of this report.

Method and Material

Thirty-two patients were treated with Dibenzyline, 18 being hospitalized initially and then followed in the outclinic and 14 being treated in the outclinic during the entire period of the study. Most of the hospitalized patients had symptoms of hypertensive encephalopathy, and all had severe hypertensive vascular disease (53 per cent had diastolic pressures above 140). Three patients had malignant nephrosclerosis and uremia. Two others were in uremia due to glomerulonephritis and pyelonephritis, respectively. Nine additional patients had significantly impaired renal function as indicated by the laboratory tests employed. Previous cerebrovascular accidents had occurred in 9 patients. Heart failure had been present in mild degree in 7 patients, and 5 gave a history of angina pectoris, but neither of these symptoms was present at the time of administration of Dibenzyline. Only 12 patients were free of any major complications associated with hypertension.

Each patient had a routine history and physical examination, serologic test, complete blood count, urinalysis, fundus examination, teleroentgenogram of the chest, 12-lead electrocardiogram and benzodioxane test. Renal function was studied by means of phenolsulfonephthalein (P.S.P.) excretion and determinations of urine specific gravity and blood urea nitrogen. In some cases creatinine and inulin clearances were done. Cerebral blood flow before and after intravenous administration of Dibenzyline was studied in 4 patients, the method of Kety and Schmidt[1] being used.

The control blood pressures on the outpatients were determined by the average of repeated observations over several months, during which weekly visits were made to the clinic. On each clinic visit the blood pressure was taken at the time the patient registered, again when the patient was interviewed and examined by the physician (investigator) and again three or four hours after registration, just before the patient returned home. Placebos were given for several weeks before the administration of Dibenzyline. A shorter period of observation was necessary to determine the control blood pressures in the hospitalized patients. Both supine and standing pressures were recorded after blood-pressure stabilization had been reached in the respective positions. Mean blood pressures were calculated on the basis of diastolic pressure plus a third of the pulse pressure. The patients were arbitrarily divided into two groups on the basis of diastolic blood pressure: those with pressures above and those with pressures under 140. A decrease of 20 in the mean blood pressure in either the supine or the standing position was considered a significant hypotensive response to the medication tested.

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¶Kindly supplied by Smith, Kline and French Laboratories, Incorporated, Philadelphia.

Dibenzyline was administered in 20-mg. gelatin capsules. The outpatients were given 20 mg. every five hours (with meals and at bedtime), and the dose was increased at weekly intervals until the blood pressure fell or toxic manifestations occurred. Hospitalized patients were given a 20-mg. increase in dose every four hours until a hypotensive effect or toxic manifestations occurred. After the effective dose was determined in these patients, the dose being increased at weekly intervals until a satisfactory response or toxicity occurred. Thirteen patients who had previously failed to obtain adequate reduction in blood pressure with hexamethonium alone were given hexamethonium and Apresoline together. In this group, when the maximum tolerated dose of hexamethonium failed to lower the pressure adequately, Apresoline was begun in a dosage of 25 mg. four times daily and increased

TABLE 1. *Blood-Pressure and Clinical Response of 32 Hypertensive Patients Treated with Dibenzyline for Three Months.*

Case No.	Age	Dose*	Standing Blood Pressure				Supine Blood Pressure				Pulse Change	Result of Therapy
			Control		Dibenzyline		Control		Dibenzyline			
	yr.	mg.	systolic	diastolic	systolic	diastolic	systolic	diastolic	systolic	diastolic		
Diastolic blood pressure more than 140 (12 out of 17 patients responding):												
1	58	120	250	150	154	114	250	150	172	110	+30	Good; patient still on drug.
2	28	360	260	180	240	180	290	160	270	140	+ 6	Patient died of uremia
10	38	80	200	160	150	90	270	170	150	90	+24	Drug discontinued because of syncope and nausea
15	25	160	190	130	110	70	190	140	140	90	+12	Good [illegible]ult; patient still on drug
16	58	120	220	140	120	90	240	140	180	110	+18	Drug [illegible] continued because of dizziness
17	58	80	220	140	120	90	220	140	130	90	+ 8	Good result; patient still on drug.
18	62	80	180	140	100	85	180	132	140	90	+22	Drug discontinued because of dizziness
19	58	120	250	150	154	114	250	150	172	110	+30	Good result; patient still on drug.
25	58	40	194	142	118	100	200	140	170	130	+40	Good result; patient still on drug.
27	47	200	300	164	220	120	300	150	320	150	+40	No serious side effects
28	47	200	220	150	152	126	220	130	172	124	+26	No serious side effects
4	59	100	210	140	140	90	200	110	190	110	+36	Drug discontinued because of tachycardia
Mean	50	138	225	149	148	106	234	143	184	112	+24	
Diastolic blood pressure less than 140 (11 out of 15 patients responding):												
3	54	80	160	100	90	70	190	110	130	90	+32	Patient died of uremia
5	57	120	200	130	160	100	210	130	200	120	+34	Patient still on drug
12	63	120	180	130	110	80	190	120	140	100	+16	Patient still on drug
13	58	200	200	100	160	80	210	120	180	110	+20	Drug discontinued because of tachycardia
14	42	120	140	110	130	90	170	130	140	110	+16	Blood pressure remained normal after discontinuance of drug
21	47	120	170	110	120	90	180	104	182	120	+12	Patient failed to return (tachycardia)
23	74	240	192	80	136	76	200	100	180	96	+ 6	Drug discontinued because of nausea and diarrhea
26	56	80	216	130	118	80	240	120	154	98	+40	Patient still on drug (diarrhea)
29	40	20	180	130	140	110	180	130	170	120	+28	Drug discontinued because of tachycardia
31	47	240	220	120	140	80	230	130	180	110	+50	Drug discontinued because of tachycardia and angina
32	26	60	260	130	120	60	260	130	230	120	+30	Patient still on drug; attacks of syncope.
Mean	51	127	193	115	129	83	205	120	171	109	+26	

*Given 4 times a day.

they were given the same amount of drug before each meal and at bedtime.

A similar group of 54 outpatients was treated with hexamethonium, the same method of titration that was used on the outclinic patients receiving Dibenzyline being followed. These patients initially received 250 mg. of the drug every five hours, and the dose was increased at weekly intervals until a satisfactory hypotensive response or toxic symptoms supervened. Sixty-one outclinic patients were given extracts of *Veratrum viride*. Thirty received Veriloid, and 31 received Anatensol. Here, again, the dosage schedule was established by titration. Fifty-two patients were treated with Apresoline. A titration procedure was also used with this drug, until a satisfactory hypotensive response or toxic effects occurred.

Results of Therapy with Dibenzyline

The blood-pressure response to the administration of Dibenzyline is shown in Table 1. It is quite evident that the drug is a potent hypotensive agent. The blood-pressure responses of 17 patients with diastolic pressures of 140 or more were as follows: 12 out of 17 patients (71 per cent) responded to the drug with a reduction in the mean blood pressure of 20 or more, averaging 37 in the supine and 54 in the standing position. Pressures in the supine position, which were not significantly lowered in 3 of the 12 patients, fell to a normal range (150 systolic,

100 diastolic, or lower) in 4 patients (24 per cent), and standing pressures were decreased to this level in 7 (41 per cent) of the patients in this group. Eleven (73 per cent) out of the 15 patients with diastolic pressures under 140 responded to the drug. The average fall in mean pressure of the patients in this group who responded was 19 in the supine and 42 in the standing position. In 8 patients (53 per cent) the blood pressure fell to 150 systolic, 100 diastolic, or below in the standing position, but in the supine position it reached this level in only 2.

The average dose of the drug required by the responsive group was 138 mg. four times a day in patients with diastolic pressures over 140 and 127 mg. four times a day in those with diastolic blood pressures under 140, indicating little difference in the effective dose in the two groups. The largest dose used in the responsive group was 360 mg. four times daily. A few patients required as little as 20 to 60 mg. four times a day.

TABLE 2. *Average Blood-Pressure Response to Dibenzyline Compared to That of Other Hypotensive Drugs.**

DRUG	NO. OF PATIENTS	RESPONSIVE PATIENTS†					
		CONTROL BLOOD PRESSURE		BLOOD PRESSURE ON DRUG IN SUPINE POSITION		BLOOD PRESSURE ON DRUG IN STANDING POSITION	
		systolic	*diastolic*	*systolic*	*diastolic*	*systolic*	*diastolic*
Initial diastolic pressure of more than 140:							
Dibenzyline	12	234	143	184	112	148	106
Hexamethonium	13	227	150	182	115	161	106
Hexamethonium and Apresoline‡	3	242	149	156	96	126	63
Apresoline	4	234	150	190	116	174	115
Veriloid (by mouth)	8	259	156	200	123	Same	
Anatensol	2	255	150	200	120	Same	
Initial diastolic pressure of less than 140:							
Dibenzyline	11	205	120	171	109	129	83
Hexamethonium	33	205	126	172	106	142	72
Hexamethonium and Apresoline‡	4	204	131	167	107	140	98
Apresoline	13	202	122	168	103	162	106
Veriloid (by mouth)	7	199	122	161	97	156	98
Anatensol	4	192	124	161	101	158	99

*Follow-up period on the patients receiving the various drugs was 3 to 9 months.
†Decrease in mean blood pressure of 20 or more either supine or upright position.
‡Patients without adequate response to hexamethonium alone.

An invariable effect of the drug in patients who obtained a reduction in blood pressure was an increase in the pulse rate on standing. The increase averaged about 20 beats per minute, but an increase of 30 to 40 beats was not uncommon. Patients whose blood pressures failed to fall showed less tachycardia. Clinically, the rapid heart action was very disturbing and necessitated the discontinuation of the drug in several patients. In 3 patients, angina occurred in association with the rapid heart rate, and in another patient, frank cardiac failure supervened.

The effect of Dibenzyline on cerebral function was of interest. Many of the patients had symptoms of encephalopathy before treatment. With reductions in the blood pressure, these patients were greatly relieved. On ambulation, however, many patients complained of dizziness, lightheadedness, forgetfulness and inability to concentrate. Syncope occasionally occurred, particularly if the patient stood motionless for some time. Wrapping the legs of several patients did not seem to help. These symptoms were sufficiently distressing to warrant the discontinuation of the drug in 3 patients. Although 9 patients had experienced previous cerebral accidents, no case of cerebral thrombosis occurred during therapy. Studies of cerebral blood flow in 4 patients in the supine position indicated that no alteration in cerebral hemodynamics (except decreased cerebrovascular resistance) occurred with moderate reduction in blood pressure. The effect on cerebral blood flow in the upright position was not determined.

No adverse effect on renal function was observed after Dibenzyline, either by the use of the clinical laboratory studies or by the use of clearance technics (para-aminohippurate and inulin). There was no evidence that Dibenzyline altered the uremic state, and 4 of the 5 patients with uremia died. None of them improved clinically, although 2 responded with a fall in mean blood pressure of more than 20. A moderate gastrointestinal hypermotility was occasionally encountered. Whether this was due to decreased sympathetic tonus or local irritation from the drug cannot be stated. One patient was forced to stop the drug for this reason. Nasal congestion and constriction of the pupil, although almost universally present, were not very disturbing to the patients. By the end of three months, the drug had to be discontinued in 8 of 23 patients who had obtained an initial hypotensive effect (mean blood-pressure reduction of more than 20) because of side effects such as tachycardia, dizziness, syncope, gastrointestinal irritation and angina. The distressing side effects in these patients could not be eliminated by variation in dosage or interval of administration even under hospital conditions. Only 11 of the 23 patients felt sufficiently benefited

to continue the therapy for more than three months. Two of the 23 responsive patients died (Cases 2 and 3), and in 1 (Case 14) the blood pressure remained normal after the drug had been discontinued. One patient discontinued therapy of her own volition.

An analysis of the nonresponsive patients indicates that 4 of the 5 patients with diastolic pressures over 140 died within a month of the therapeutic trial with Dibenzyline. They tolerated an average of 276 mg. of the drug four times daily, twice the average dose in the responsive patients, before therapy was interrupted. Failure to respond constituted a grave omen in this group of patients. In the unresponsive group (4 patients) with control diastolic pressures less than 140, the average dose of Dibenzyline was 135 mg. four times a day before severe toxic symptoms necessitated discontinuance of therapy. This was approximately the same average dose as that for the responsive patients. The drug was discontinued in 2 of the 4 patients because of angina pectoris, in 1 because of cardiac failure and in 1 because of cerebral manifestations.

TABLE 2 (*Concluded*).

DRUG	NO. OF PATIENTS	UNRESPONSIVE PATIENTS: CONTROL BLOOD PRESSURE		BLOOD PRESSURE ON DRUG IN SUPINE POSITION		BLOOD PRESSURE ON DRUG IN STANDING POSITION	
		systolic	*diastolic*	*systolic*	*diastolic*	*systolic*	*diastolic*
Initial diastolic pressure of more than 140:							
Dibenzyline	5	218	150	224	152	187	140
Hexamethonium	2	232	156	218	151	213	153
Hexamethonium and Apresoline‡	3	298	162	221	158	239	150
Apresoline	6	241	152	234	143	227	141
Veriloid (by mouth)	5	210	124	204	118	202	121
Anatensol	6	225	147	213	138	209	142
Initial diastolic pressure of less than 140:							
Dibenzyline	4	203	118	194	118	173	107
Hexamethonium	6	201	124	187	120	199	118
Hexamethonium and Apresoline‡	3	224	124	207	112	191	122
Apresoline	29	204	135	203	129	197	121
Veriloid (by mouth)	10	200	124	196	118	Same	
Anatensol	19	195	118	189	115	Same	

RESULTS WITH OTHER HYPOTENSIVE DRUGS

A comparison of the response to Dibenzyline and other hypotensive drugs used in this clinic is given in Table 2. The clinical material is comparable, and the various drugs were administered under the same conditions with the use of similar "titration methods." Hexamethonium, an orally effective ganglionic blocking agent, was used on 54 patients, who were observed for six to nine months. All but 8 responded with a fall in the mean blood pressure of 20. Blood-pressure reduction was more marked in the standing position. The blood pressure in the upright position was reduced to 150 systolic, 100 diastolic, or lower in 27 patients, but this level was only reached in 5 patients in the recumbent position. Side effects were chiefly those of parasympathetic blockade and were rarely serious enough to cause discontinuation of therapy. No tachycardia was experienced, probably because of concurrent ganglionic blockade of the sympathetic nerve supply of the heart. Syncope occurred in 7 patients, and dizziness on standing in 22 patients, owing to excessive reduction in blood pressure in the upright position. These manifestations could usually be prevented by careful regulation of dosage, and the patients learned to reduce the amount of drug ingested when warning symptoms occurred. In a few cases blood-pressure determination by the patient himself was successfully undertaken, and the dosage regulated accordingly. No patient experienced angina or coronary thrombosis while taking the drug. Indeed, symptomatic improvement occurred in 11 out of 14 patients with angina pectoris. Symptomatic relief of hypertensive headaches occurred in 18 out of 22 patients, and retinopathy improved in 7 out of 11 patients with Grade 3, and 9 of 10 patients with Grade 4 changes in the eye grounds. Renal function was not altered, but the drug must be administered with great caution in patients with impaired renal function and nitrogen retention or the azotemia may progress and serious overdosage may occur from retention of the drug.

Fifty-two patients treated with Apresoline were followed for one to two years. A reduction of mean blood pressure of 20 or more was obtained in 17 of the 52 patients treated, but only 8 of these could be maintained on therapy for a year or more. Of the 8 who continued on therapy, 4 continued to show a significant hypotensive response. Poor response was largely due to side effects, which necessitated discontinuance of the drug in most of the patients. These were chiefly tachycardia, nausea, vomiting and diarrhea. Neurologic com-

plaints such as hypesthesia and hyperesthesia were prominent side reactions after the drug had been given for prolonged periods. Headache was a frequent symptom early in therapy, but this subsided spontaneously after several weeks. Electrocardiographic abnormalities (notching and inversion of the T wave and ST-segment depression) occurred in 5 patients. This was associated with tachycardia.

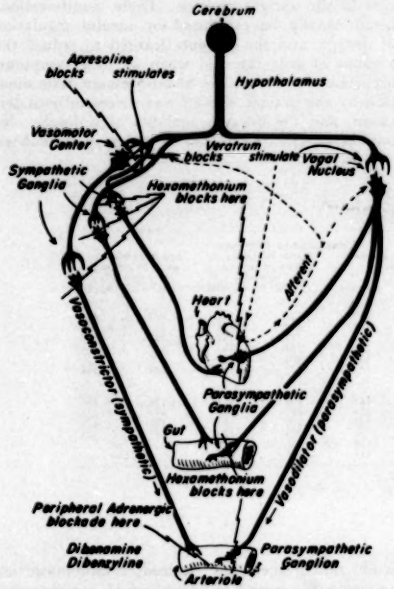

FIGURE 1. *Diagrammatic Representation of the Site of Action of Some of the More Active Hypotensive Drugs on the Autonomic Nervous System.*

The jagged lines indicate the point at which the various drugs produce blockade. The heavy solid lines on the left indicate the sympathetic components of the autonomic nervous system, and the solid lines on the right the parasympathetic outflow. The fine broken line indicates the point of action and the afferent pathway for the reflex component of the vasodepressor action of the Veratrum viride *compounds.* Veratrum viride *also has a direct central action, blocking off vasoconstrictor impulses before they reach the peripheral component of the sympathetic nervous system. Hexamethonium blocks ganglionic transmission of impulses over the same system. Dibenzyline blocks off the transmission of impulses from the postganglionic fiber to the arteriole.*

When Apresoline was added to the therapy of 13 patients who had shown an inadequate response to hexamethonium alone, a good clinical response was obtained in 7. The usual side effects encountered when Apresoline is used alone were markedly lessened.

Anatensol* and Veriloid, two *Veratrum viride* compounds, were tested on 31 and 30 patients respectively. A satisfactory response was obtained in 6 of 31 patients treated with Anatensol and in 15 of 30 patients treated with Veriloid. The blood pressure was reduced to normal ranges (less than 150 systolic, 90 diastolic) in only 3 per cent of patients receiving Anatensol and 7 per cent of those receiving Veriloid. This poor response was due to the high incidence of nausea and vomiting. Since the margin of difference between the toxic and therapeutic response is narrow, it is difficult to maintain patients on these drugs even if a satisfactory hypotensive effect is obtained, for a very small difference in the absorption of the drug may precipitate emesis. No difference in the blood pressure in the upright and recumbent positions was encountered.

*Now known as Vergitryl.

DISCUSSION

Pharmacology

Dibenzyline (N-phenoxyisopropyl-N-benzyl-β-chlorethylamine) is a substituted β-chlorethylamine derivative with properties similar to those of Dibenamine.[2,3] It is capable of completely blocking excitatory responses of epinephrine, ephedrine, norepinephrine, Neo-synephrine and sympathetic-nerve impulses at the effector organ with the exception of those that act on the myocardium. There is no blockade to transmission of impulses through the ganglions, and no direct effect on smooth muscle. The drug does not stimulate the vagus nerve. When it is given intravenously (0.25 to 0.5 mg. per kilogram of body weight[4]) the hypotensive effects occur after a short latent period; the pressure often falls to dangerously low levels if the drug is not administered with great caution. After blockade, epinephrine and norepinephrine produce a sharp reduction in blood pressure (blood-pressure reversal). Ephedrine, Neo-synephrine and norepinephrine are ineffective as vasopressor agents against overdosage of Dibenzyline. The only effective measure is to tilt the patient in a head-down position. Dibenzyline, in addition to being more potent than Dibenamine, produces little central-nervous-system stimulation.[5] Owing to its greater potency and decreased gastric irritation, it can be administered orally.[6] After oral administration, the maximum hypotensive response occurs in about two hours, and blockade, once established, lasts twenty-four to thirty-six hours. Gastrointestinal hypermotility is often noted. Nasal stuffiness and constriction of the pupils also occur. No toxic effect on the hematopoietic system has been noted,[6] although the drug is chemically related to the nitrogen mustards.

The point of action of Dibenzyline on the autonomic nervous system as well as the other hypotensive drugs used in the current study can be visualized in Figure 1. Dibenzyline blocks peripherally at the sympathetic neuroeffector (vasoconstrictor) site. Hexamethonium produces hypoten-

sion by blockade of the sympathetic nerve fibers at the ganglionic synapse.[7] It also causes a wide range of other responses because of parasympathetic ganglionic blockade — that is, a reduction of gastric and intestinal motility, gastric acidity and salivation, a decrease in bladder tonus and so forth. Although the pharmacology of Apresoline is not well understood, there is evidence that the hypotensive effect is of central origin.[8] Schroeder[9] found that a combination of hexamethonium and Apresoline was highly effective in reducing blood pressure. Some of the undesirable effects of Apresoline are due to a sympathomimetic action of the drug on the heart (tachycardia and increased cardiac output). This can be blocked by hexamethonium or sympathectomy.[10] A more pronounced hypotensive effect is often obtained with combined therapy.

Veriloid and Anatensol are semipurified extracts of *Veratrum viride*. These drugs contain several purified alkaloids, and, although their composition is not identical, their pharmacologic properties are similar. The hypotensive effect is due to stimulation of afferent-nerve endings in the left ventricle, lungs and carotid sinus, which run from these areas to the medulla via the vagus nerve. This excitation produces reflex hypotension and bradycardia.[11, 12] A central hypotensive action has also been demonstrated in dogs by perfusion of the isolated head.[13, 14] The nausea and vomiting occurring with purified alkaloids is of central origin.[15] Atropine blocks the bradycardia, but does not affect the vomiting or hypotension. The hypotensive effect can be reversed by norepinephrine, Neo-synephrine and other sympathomimetic drugs.

Clinical Application

Haimovici, Moser and Krakauer[16] reported favorable results in 16 of 22 hypertensive patients treated with enteric-coated Dibenzyline. Side effects were minor and easily controlled by variation in dosage. Moser and his associates[17] treated 11 patients. A significant fall in diastolic pressure occurred in 5 patients in the recumbent and in 9 in the standing position. Side effects, though annoying, did not contraindicate the use of the drug. Redisch et al.[18] found reduction in blood pressure in 4 of 5 hypertensive patients. Corcoran, Taylor and Harrison,[19] however, observed no reduction in blood pressure in 7 of 8 hypertensive patients.

In the present study Dibenzyline proved to be a powerful hypotensive agent. Its clinical usefulness, however, appears to be limited because of undesirable side effects. In common with other peripheral adrenergic blocking drugs, a marked tachycardia is associated with the fall in blood pressure. The increase in heart rate is probably a reflex response to the fall in blood pressure (Morey's Law) since Dibenzyline fails to block the myocardial effects of sympathetic stimulation. Although the tachycardia associated with reduction in blood pressure was annoying enough to necessitate discontinuation of therapy in only 4 cases, 4 additional patients showed impaired myocardial function, owing to either decreased coronary blood flow or increased cardiac output. Three patients had angina, and another had cardiac failure while on therapy. No other reason for the development of these difficulties could be elicited. Moser[17] has reported the occurrence of an ischemic pattern in the electrocardiogram of a patient treated with Dibenzyline. It seems likely that the tachycardia rather than the hypotension is responsible for the precipitation of coronary insufficiency and heart failure in these patients, for when a similar degree of hypotension is produced by hexamethonium no cardiac acceleration occurs and angina is rarely precipitated. We believe that Dibenzyline should not be used in the presence of coronary insufficiency or heart failure. Hexamethonium, which acts by producing ganglionic blockade, and *Veratrum viride* extracts, which act centrally, do not cause tachycardia or an increase in cardiac output. Hence, they can be used in patients with heart disease.

Another group of significant side effects included cerebral manifestations. Although relief of headache and other symptoms of hypertensive encephalopathy were noted in patients who responded well to the drug, dizziness and syncope were frequently observed, necessitating discontinuation of therapy in 3 patients, despite careful attention to dosage. A number of the patients complained of mental dullness and decrease in memory, but for the most part, these symptoms were relieved on lying down. This may have been due to overzealous therapy and excessive reduction in blood pressure in some cases, but not in all. Although dizziness and syncope in the upright position also occurred in patients treated with hexamethonium, vasoconstrictor reflexes for postural adjustment of blood pressure were better preserved, and we found it easier to maintain a good hypotensive effect without cerebral manifestations while the patient was standing. Centrally acting drugs (*Veratrum viride* and Apresoline) have the advantage of producing a minimal amount of orthostatic hypotension with preservation of the adaptive postural reflexes. Despite these difficulties with Dibenzyline, no cerebral accidents occurred in our series, although 9 patients had sustained previous cerebrovascular accidents. It is our opinion that hypotensive drugs in general protect against cerebral accidents by relieving the head of pressure and dilating the cerebrovascular bed. However, as a precautionary measure, the blood pressure in the standing position probably should not be lowered much below 150 systolic, 100 diastolic, in patients who have had a high pressure or symptoms of cerebral arteriosclerosis.

In our experience the ganglionic-blocking drug hexamethonium, alone or in combination with

Apresoline, is the agent of choice in the treatment of severe essential hypertension. Dibenzyline should be reserved for patients who are intolerant or do not respond to these drugs. At present, *Veratrum viride* compounds have too low a therapeutic index to be very useful by the oral route, but if a similar type of compound without the emetic properties could be developed it might well be superior to other compounds available since these drugs do not produce orthostatic hypotension. In the use of hypotensive drugs, great care must be taken to preserve the circulation in the critical vascular beds. We believe that a safe level of blood pressure is about 150 systolic, 100 diastolic, in the upright position. Even with marked but unavoidable hypotension encountered in a clinic population, no serious accidents have occurred. Certainly, longer observation will be necessary for thorough assay of the hazards as well as the benefits of this type of therapy.

Summary

Dibenzyline has been used in the treatment of 32 patients with severe essential hypertension. Twenty-three patients (72 per cent) responded with a fall of more than 20 in the mean blood pressure. In the standing position, the blood pressure decreased to less than 150 systolic, 100 diastolic, in 47 per cent of the patients.

There was a high incidence of distressing side effects in the upright position, chiefly tachycardia, and symptoms of decreased cerebral blood flow. Only 11 (34 per cent) patients felt sufficiently benefited to continue therapy for more than three months.

A comparison with other hypotensive agents indicates that the ganglionic-blocking drug hexamethonium is the agent of choice. Combined therapy with Apresoline was effective in about 50 per cent of the patients who did not obtain an adequate reduction in blood pressure with hexamethonium alone.

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CLINICAL AND PHONOCARDIOGRAPHIC OBSERVATIONS ON THE FLINT MURMUR*

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IT is an established clinical observation that certain patients with aortic regurgitation have an apical presystolic murmur without mitral stenosis demonstrable at autopsy. This phenomenon was originally described ninety years ago by the American physican, Austin Flint,[1] who made his first observations in New Orleans. From the original report in 1862 it is difficult to determine whether Flint was describing a murmur in mid-diastole or in presystole. This was due to the terminology used in his time for describing cardiac murmurs. However, there is little doubt from a later report (1886)[2] that he was describing a murmur in presystole. This murmur was the type regarded during the latter part of the nineteenth century as characteristic of mitral stenosis. When rheumatic fever and syphilis are suspected in the same person, the discovery of an apical presystolic murmur in a patient with aortic regurgitation presents a problem in differential diagnosis.[3]

Observations on the timing and character of the Flint murmur have been clinical and descriptive and thus subjective. Since the development of phonocardiography it has been possible to demonstrate and study these murmurs objectively with reference to timing, intensity and frequency. Weiss and Joachim[4] recorded a Flint murmur phonocardiographically in 1911, but few of these murmurs have been recorded and reported in the medical literature.[5-8] Luisada[7, 8] considers the Flint murmur as an auscultatory illusion in most cases.

The cause of this murmur has been the subject of much speculation. A glance at the various explanations[9-20] and comments regarding the Flint murmur (Table 1) demonstrates that the etiology remains obscure. Correlation between clinical observations and anatomic findings at autopsy has not been particularly rewarding in providing an explanation acceptable by most observers. It is desirable to record these murmurs objectively so that a correlation can be made between the phonocardiogram and the anatomic findings at autopsy.

The purpose of this report is to present a study of 14 patients who had aortic regurgitation and presystolic vibrations demonstrable by phonocardiogram. It is realized that for a complete understanding of this phenomenon at least two conditions should be fulfilled: a large number of such murmurs should be recorded for clinical and clinicopathological correlation and a technic to determine the origin of such vibrations should be devised.

Method of Study

The majority of the 24 patients in this study were selected from the syphilis outpatient department. All patients with a clinical diagnosis of syphilitic heart disease had a positive blood Hinton test[21] for syphilis, and none gave a history of rheumatic fever. Some of them had no symptoms referable to the cardiovascular syphilis. The majority of patients selected for phonocardiography were thought to have a Flint murmur. In about a quarter of the cases no definite murmur was detected by auscultation, but because of the degree of aortic regurgitation and the magnitude of the pulse pressure it was thought that presystolic vibrations might be demonstrable by phonocardiography. One patient (Case 14) with coarctation of the aorta, hypertension and aortic regurgitation resulting from a bicuspid aortic valve is included; she had been receiving protoveratrine by mouth for several months, with symptomatic relief from congestive heart failure. The logarithmic response to resemble human hearing was used to register the phonocardiogram.[22] The patients were in the recumbent position when the phonocardiograms were made.

Results and Discussion

The murmur described by Flint and his contemporaries as characteristic of mitral stenosis was termed the "mitral direct murmur" and noted as presystolic in timing. This murmur was attributed to the "mitral direct current" of blood passing through the mitral valve, and it was considered to be a result of auricular contraction. In fact, some observers suggested that it be termed the auricular systolic murmur. It is apparent, therefore, that most clinicians of those days were not aware of the portion of diastole in which ventricular filling precedes the auricular contraction, now termed the "rapid inflow phase" of diastole. This occurs in the early or mid-diastolic period, depending on the length of diastole, and is sometimes referred to as the protodiastolic period. It begins at the moment the mitral valve opens, which is frequently audible as a snapping sound in patients with mitral stenosis. With a normal sinoauricular rhythm the usual murmur of mitral stenosis has two components: the mid-diastolic period, during which there may be an accentuation of the murmur; and the presystolic

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period, attended with a crescendo murmur attributable to the auricular contraction (Fig. 1).

The timing of the Flint murmur has been described as both presystolic and mid-diastolic, the majority of observers considering it to be presystolic (Table 2). In patients with aortic regurgitation the apical murmur in early or middle diastole may be of two types: a low-frequency murmur resulting from left-ventricle dilatation heard in mid-diastole; and a medium-frequency or high-frequency, diminuendo murmur, which is transmitted to the apex from the aortic valve and has the characteristics of aortic regurgitation. The latter was the common murmur evident in the phonocardiograms of this study and accounts for the early diastolic to mid-diastolic murmur heard in most of these patients.

The phonocardiograms of 24 patients were studied, and 14 were found to demonstrate vibrations in the presystolic phase of diastole. The murmur was considered presystolic if it began before the Q wave of the electrocardiogram. This rigid criterion clearly differentiates these patients from those with crescendo first heart sounds that may give an auscultatory illusion of a presystolic murmur.[24]

All these patients had wide pulse pressures and aortic diastolic murmurs. In 13 cases the clinical

TABLE 1. *Various Explanations Offered for the Flint Murmur.*

AUTHOR	DATE	EXPLANATION
Flint[1, 2]	1862 and 1886	"The distention of the ventricle is such that the mitral curtains are brought into coaptation. . .and when the auricular contractions take place the mitral direct current passing between the curtains thus in contact with each other throws them into vibration and gives rise to the characteristic blubbering murmur."
Guiteras[3]	1885	"The breakwater of the aortic valve had been removed, and mitral valve was shut down by the recoil of the arterial pressure. The bicuspid in other words, did the work of the semilunar valves, and kept the reflux of blood from rushing back from the efferent to the afferent cavities of the heart. The mitral valve was closed, therefore, and blood driven through its long chink by the hypertrophied auricle produced the diastolic presystolic murmur."
Sansom[10]	1892	"The vibrations might be directly communicated by the regurgitant stream from the aorta to the great mitral curtain. The nearness of the posterior segment of the aortic valve may well account for such vibrations. These vibrations may attain only to the intensity and rapidity sufficient to cause a murmur somewhat late in the diastolic period. The force of the auricular systole would necessarily amplify and intensify such vibrations of the free edge of the flap until the commencement of ventricular systole."
Broadbent[11]	1899	"It is conceivable that the murmur may be due to this flap of the mitral valve being thrown into vibration by the regurgitant stream from the aorta, the vibration being conducted to the apex by the chordae tendineae and papillary muscles, or, on the other hand, that the backward rush of blood from the aorta prevents the complete falling back of this flap of the mitral valve so that some actual obstruction of the mitral orifice results, giving rise to a presystolic murmur."
Thayer[12]	1901	"In conclusion, one may be justified in saying that in uncomplicated aortic insufficiency a rumbling, echoing, presystolic or mid-diastolic murmur limited to the region of the apex of the heart is very common, occurring, when carefully looked for, in fully half of the cases. The characters of this murmur are in no way different from that commonly observed in true mitral stenosis, with the exception of the fact that it is usually of moderate intensity."
DaCosta[13]	1908	"Owing to the enlargement of the ventricular cavity, the anterior cusp of the mitral valve is displaced during diastole, from its accustomed mural position, so that it projects into the rising tide of blood within the ventricle, and consequently becomes the target of two blood streams coming from opposite directions — one regurgitating through a leaky aortic orifice and the other issuing (normally) from the mitral opening. By this mechanism vibrations of the cusp are set up toward the middle or end of diastole, with the generations of a presystolic murmur and thrill appreciable at the apex."
Cabot[14]	1915	"How it is that a presystolic murmur can be produced at the apex in cases of aortic regurgitation has been much debated but remains unknown."
Huffman[15]	1918	"The thrill and presystolic murmur at the mitral area due to the vibrations set up by churning of the blood in the ventricle by the small stream squirted into it from the small mitral orifice by the force of the hypertrophied and distended auricle in the case of mitral stenosis; or squirted back from the leaky aortic valve into the blood in the ventricle in the case of aortic regurgitation. In both cases the stream is squirted with considerable force but it is only toward the end of diastole when the ventricle is practically full that the stream meets with considerable resistance. The stream shoots across the blood-filled ventricle in the direction of the apex, where it strikes the wall of the heart, causing the localized thrill and rumble."
Hirschfelder[16]	1918	"This rumble is in every respect similar to that of mitral stenosis, and it is extremely difficult to determine whether the latter is absent. . .The writer has been able to show on the excised heart, by the method of Baumgarten and Gad, that although the mitral valve usually opens along its entire extent, yet when the pressure within the ventricle is increased, the separation of the cusps occurs at only a small portion of the line of closure."
White[17]	1926	"This Austin Flint murmur is best explained by relative narrowness of the normal mitral orifice when the left ventricular cavity is much dilated. It is, therefore, found occasionally not only with well marked aortic regurgitation but also with left ventricular dilatation due to other causes."
Herrmann[18]	1926	"The regurgitant blood stream passing the damaged posterior cusp would tend to carry the anterior mitral flap upward and produce a functional obstruction in the mitral orifice."
Gouley[19]	1941	"In ten patients who had Flint murmurs incidental to aortic regurgitation a characteristic deformity of the right aortic leaflet was found at necropsy. This consisted of a concave, cup-shaped deficiency of the inner portion of the leaflet, so situated as to divert or 'groove' the regurgitating blood toward the lower portion of the anterior mitral curtain. The latter exhibited on its ventricular aspect a variable degree of endocardial thickening which was interpreted as a frictional sclerosis."
Carroll[20]	1951	"Three patients had ruptures or perforations of the posterior cusp alone. All of these patients had Austin Flint murmurs. In this series then, an Austin Flint murmur was present only when the posterior cusp was involved. This finding supports the theory that the Austin Flint murmur originates from deflection of the aortic leaflet of the mitral opening due to the regurgitating blood stream to impinge on the mitral aortic leaflet, whereas injury of the left or right coronary cusps would deflect the regurgitating blood toward the ventricular wall."

diagnosis was syphilitic heart disease with aortic regurgitation and a positive blood Hinton test for syphilis (Table 3). Two of the 14 patients were studied at autopsy, and the mitral valve was found to be normal in each case. One of these patients had aortic regurgitation resulting from a bicuspid aortic valve in association with coarctation of the aorta.

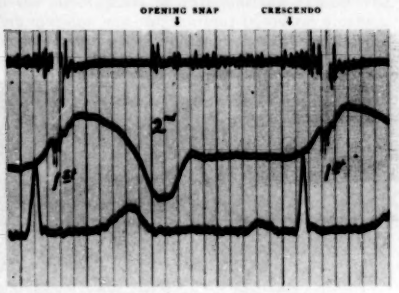

FIGURE 1. *Diastolic Murmur of Mitral Stenosis, Demonstrated with Presystolic Accentuation.*

Phonocardiogram, apex cardiogram and electrocardiogram are illustrated from above downward. The major component of the first heart sound is delayed, as is characteristic of mitral stenosis, beginning 0.09 second (upper limits of normal, approximately 0.08 second) after the Q wave of the electrocardiogram. The opening snap of the mitral valve is synchronous with the valley in the apex cardiogram that just precedes the rapid-inflow phase. A third sound is visible, beginning at the end of the rapid-inflow phase of the apex cardiogram.

Cardiac enlargement has been regarded as an important feature by Flint and others in patients with diastolic murmurs. The majority of the 14 patients demonstrated a variable degree of cardiac enlargement by the usual teleroentgenogram, but in 3 cases the heart size was normal. No correlation between the clinical audibility of the presystolic murmur and the size of the heart was evident. Left-ventricle dilatation is apparently not essential for the production of the Flint murmur but may predispose the heart to such a murmur. Dilatation of either the right or the left ventricle is at times associated with a mid-diastolic low-frequency rumbling murmur but is not usually followed by a crescendo during the presystolic period.[25]

In 3 patients no presystolic murmur was detected by auscultation. The explanation for this is not clear although it is known that the Flint murmurs are usually quite localized and hence more easily overlooked. The difference of 2 or 3 cm. in the position of the stethoscope bell and the pick-up bell for the phonocardiogram could account for this discrepancy. The pick-up bell is also of larger size than the usual stethoscope bell, measuring 5 cm. in diameter.

TABLE 2. *Timing of the Flint Murmur by Various Observers.*

AUTHOR	MIDDIASTOLIC	PRESYSTOLIC
Flint[1, 2]		√
Guiteras[3]		√
Sansom[15]		√
Phear[22]		√
Broadbent[23]	√	√
Thayer[24]	√	√
DaCosta[25]		√
Cabot[26]		√
White[27]	√	√
Herrmann[28]	"Diastolic Rumbling"	
Gouley[29]		√
Carroll[30]		√

TABLE 3. *Audibility of the Flint Murmur in Relation to Heart Size and Blood Pressure.**

CASE NO.	FLINT MURMUR BY AUSCULTATION†	CARDIAC ENLARGEMENT BY X-RAY STUDY	BLOOD PRESSURE
	0 to ++++	0 to ++++	
2	+++	+++	200/70
8	++	0	210/70
9	++	+++	160/40
6	++	+	140/25
12	++	0	140/40-0
7	+	+	200/0
11	+	++	140/50
4	+	+	155/40
1	+	+++	150/50
13	+	++	140/40-0
14	+	+++	190/50
10	0	0	160/20
5	0	++	180/60
3	0	+	190/50-0

*There appears to be no correlation between the heart size and the audibility of the Flint murmur. In 3 cases the heart was considered of normal size.

†Localized.

The aortic regurgitant murmur heard at the apex and giving the auscultatory effect of both a mid-diastolic and a presystolic crescendo murmur of mitral stenosis was observed in Case 2 of the present series, which had been used for teaching purposes to demonstrate both the murmur of mitral stenosis and the Flint murmur. Most of the 14 phonocardiograms in this study demonstrated an early diminuendo murmur of variable duration at the apex. The mid-diastolic apical murmur heard at times in association with left-ventricle dilatation was not seen in the phonocardiograms of this study.

The high-frequency diastolic murmur in Case 12 is noteworthy, and it is apparent from the phonocardiographic tracings in Cases 2 and 12 (Fig. 2) that the presystolic portion of the murmur is of lower frequency than the early diminuendo diastolic mur-

mur resulting from the aortic regurgitation. Case 12 was also of interest in that the heart was normal in size on x-ray examination (Fig. 3), so that dilatation of the left ventricle apparently did not account for the presystolic murmur. It would be difficult to ascribe this murmur, which has a presystolic accentuation, to vibrations of an aortic-valve cusp. The concept that would best explain the presystolic accentuation of such a murmur is that vibrations of the anterior leaf of the mitral valve resulted from the two blood streams entering the left ventricle, one from the aorta, accounting for the early diastolic murmur, and the other from auricular contraction, accounting for the presystolic vibrations. The hypothesis of DaCosta[12] (Table 1), which seems the most plausible of the many advanced, best explains the observations in Case 12.

The effect of protoveratrine on the Flint murmur was noted in a patient with hypertensive heart disease secondary to coarctation of the aorta and aortic regurgitation resulting from a bicuspid aortic valve. Both the murmur of aortic regurgitation and the Flint murmur disappeared at the time of maximal protoveratrine effect. The blood pressure decreased from 190 systolic, 90 diastolic to 105 systolic, 50 diastolic, in fifteen minutes after 0.12 mg. of pro-

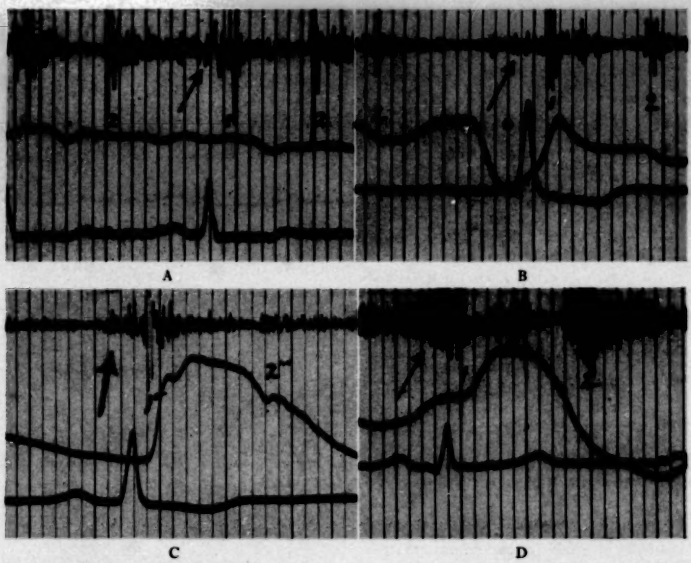

FIGURE 2. *Phonocardiogram, Venogram and Electrocardiogram Illustrated from above downward in Each of Four Cases (the Arrow Points to the Presystolic Murmur).*

A = *Tracings in Case 2. Note the murmur of higher frequency (approximately 150 cycles per second) in early diastole and the presystolic murmur of lower frequency (60 cycles per second). The murmur was Grade 3 (0 to ++++) by auscultation.*

B = *Tracings in Case 3. A presystolic murmur evident by phonocardiogram was not detected by clinical auscultation.*

C = *Tracings in Case 13. A presystolic murmur was considered to be Grade 1 in intensity by auscultation.*

D = *Tracings in Case 12. A high-frequency "musical" aortic diastolic murmur (approximately 200 cycles per second), with a presystolic crescendo murmur of lower frequency (110 cycles per second), was present. The heart was normal in size by x-ray examination.*

toveratrine had been injected intravenously. The pulse rate decreased from 100 per minute to 65. Hemodynamic studies on similar patients after intravenous administration of protoveratrine in adequate dosage have demonstrated a significant fall in cardiac output at the time of maximal effect of the drug in most patients.[26]

All observers have emphasized the difficulty if not the impossibility of distinguishing between the Flint murmur and the murmur of mitral stenosis. The presence of a sound characteristic of the opening

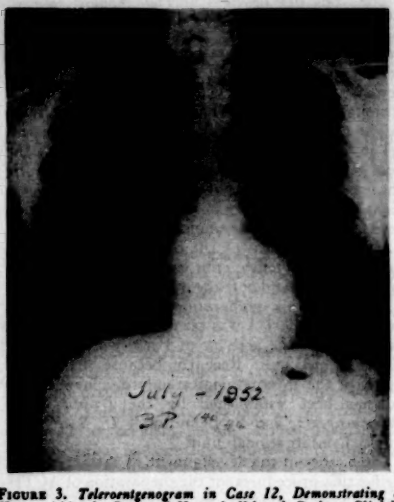

FIGURE 3. *Teleroentgenogram in Case 12, Demonstrating a Heart within the Range of Normal Although Perhaps Slightly Prominent in the Region of the Left Ventricle.*

snap of the mitral valve is in favor of the diagnosis of mitral stenosis. Accentuation of the first heart sound at the apex is common in patients with mitral stenosis and is unusual in patients with the Flint murmur. Delay in onset of the second or major component of the first heart sound beyond 0.08 second from the Q wave of the electrocardiogram is suggestive of mitral stenosis.[4, 25]

SUMMARY AND CONCLUSIONS

A study of 24 patients with aortic regurgitation is presented in which apical presystolic vibrations by phonocardiogram consistent with the Flint murmur were present in 14. A presystolic murmur was detected clinically in 11 of these patients. Autopsy revealed a normal mitral valve without mitral stenosis in 2 cases.

The mechanism by which the Flint murmur is produced remains obscure. Left-ventricle dilatation is not essential since 3 patients had a heart of normal size on x-ray examination. Vibrations arising in the anterior mitral valve leaflet best explain the murmur of relatively high frequency observed in 1 case.

Distinguishing features that help differentiate the murmur of organic mitral stenosis from the Flint murmur are an opening snap of the mitral valve and a delay in onset of the first heart sound by phonocardiogram beyond 0.08 second from the Q wave of the electrocardiogram.

We are indebted to Dr. Timothy Counihan for recording some of the phonocardiograms used in this study.

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MEDICAL PROGRESS

PHARMACOLOGIC ASPECTS OF ADRENOCORTICAL STEROIDS AND ACTH IN MAN (Continued)*

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ACTH

The classic studies of Smith[469, 470] showed that marked atrophy of the adrenal cortex followed hypophysectomy in the rat and that this change could be prevented by intramuscular implantation of rat pituitary glands. Subsequently, in 1933, four groups of investigators[471-474] reported that anterior pituitary extracts could produce adrenocortical hypertrophy in animals. Since that time there has been steady progress in the preparation of highly potent pituitary fractions possessing "trophic" activity with respect to the adrenal cortex.

NATURE of ACTH

The adrenocorticotrophic activity of pituitary extracts has been assayed principally by three methods, the first being that based on adrenal size and structure. Collip et al.[474] originally determined the effects of pituitary extracts on adrenocortical size and histologic structure in hypophysectomized rats. Subsequently, various modifications of this procedure have been introduced.[475-477] The second type is the Sayers procedure. The observation by Sayers et al.[478] that the ascorbic acid content of the adrenal gland of the rat is rapidly reduced by a single dose of ACTH led to the development of a sensitive assay method for ACTH in hypophysectomized rats.[479] Modifications designed to simplify this method when applied to a large number of animals have been introduced by Munson, Barry and Koch.[480] The third method is assay in human subjects: the adrenocorticotrophic activity of pituitary preparations has been assayed in man by the change in circulating eosinophils[248, 481, 482] after intramuscular administration of the hormone, and by the change in blood eosinophils and urinary steroids[3, 482] after intravenous infusion of ACTH. Although assay methods based on changes in adrenal weight and on ascorbic depletion have been essential in facilitating the purification of ACTH, the most reliable method of predicting the therapeutic efficacy of a given preparation has been the determination of its activity in man when it is administered by the route to be employed in clinical therapy.

After development of the Sayers assay, the first standard of potency, the preparation La-1-A,[484] was established and potency was thereafter expressed in terms of this preparation on a weight basis. Subsequently La-1-A was set up as an international standard, and the activity of 1 mg. was defined as 1 international unit. Recently, because of the short supply of the international standard, a new standard has been established by the *United States Pharmacopoeia*, and by definition 1 *U. S. P.* unit equals 1 international unit.

The history of the development of extraction and purification procedures for the preparation of ACTH has been ably reviewed by Astwood et al.[485] The first systematic study of methods for the isolation of ACTH was carried out by Collip and his associates[486-488] between 1933 and 1941. In 1942 and 1943 almost simultaneous reports by Li et al.[489, 490] and Sayers and his co-workers[491, 492] announced the isolation of ACTH in pure form. Modifications of the acetone-hydrochloric acid method of Lyons[493] were used, and purification was carried out by salting out and isoelectric precipitation. In both instances the product was regarded as a pure protein on the basis of electrophoretic and ultracentrifuge studies and its relative freedom from other pituitary hormones. The molecular weight was estimated to be 20,000, and the isoelectric point 4.7. Subsequent investigations, however, have shown that adrenocorticotrophic activity may be separated from this protein by a number of methods. In 1943 Tyslowitz[494] established the fact that ultrafiltrates of aqueous and glacial acetic extracts of porcine pituitary powder possessed corticotrophic activity. Recently, the method of ultrafiltration has been shown to be an efficient means of purifying ACTH.[495]

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The finding that the purified protein preparation of Li et al. and Sayers et al. could be subjected to partial degradation by pepsin[490] or by boiling in one-tenth normal solution of hydrochloric acid, without loss of activity, led Li[496] to suggest that the activity of the purified protein rested in a constituent peptide fragment that could be split off by these hydrolytic procedures. The average size of the constituents of the hydrolysates corresponded to peptides with 7 to 9 amino acid residues.[497] Recently, with the aid of chromatographic fractionation, Li et al.[498] obtained active fractions with mean molecular weights varying between 410 and 2800, an indication that corticotrophic activity may be possessed by a series of peptides of differing composition. Lesh and his associates,[499] using peptic digestion, obtained fractions 100 to 150 times more active than the original protein, with molecular weights estimated to be between 2500 and 10,000.

The most recent advance in the purification of ACTH has been the use of oxycellulose to adsorb the hormone from glacial acetic acid extracts of pituitary tissue.[500] By this means highly potent ACTH preparations assaying up to 100 units per milligram have been obtained. On the basis of these and other studies, Astwood et al.[455] have concluded that whereas ACTH has yet to be isolated in pure form, one can be reasonably sure that the hormone is a water-soluble, nonvolatile organic compound of modest molecular size. It is colorless, has no unique ultraviolet absorption spectrum above 240 millimicrons and contains no large lipid component and no carbohydrate, sulfur, phosphorus or heavy metal. The fact that the biologic activity is destroyed by trypsin, pepsin and carboxypeptidase suggests that one or more peptide bonds are present. The finding that there is a loss of potency upon treatment with nitrous acid or dinitrofluorobenzene indicates that one or more amino groups are essential components of the molecule. Inactivation on esterification suggests that one or more carboxyl groups are likewise essential for biologic activity. Finally, the behavior of ACTH preparations in the presence of organic acids and cation-exchange resins indicates that the hormone may possess a strongly basic group.

In a discussion of the nature of ACTH the possibility that there is more than one pituitary hormone that is trophic with respect to the adrenal cortex must be raised, in view of studies that indicate at times a lack of correlation between changes in the size of the gland, its lipid and ascorbic acid content, and its synthesis and release of a variety of steroid hormones. For example, Reinhardt and Li[501] observed that digested extracts are relatively less potent in increasing adrenal weight than undigested preparations, which are relatively less active in the Sayers' test. These findings were confirmed by Stacke-Dunne and Young,[502] who, moreover, found that a crude alkaline extract of ox anterior pituitary tissue and purified growth hormone both contain a principle that increases the weight of the adrenal glands of hypophysectomized rats despite extremely low activity in the ascorbic acid depleting test. More recently, Dixon et al.,[503] in a study of the purification of pituitary extracts by means of ion-exchange chromatography, noted that fractions with predominantly adrenal-weight-promoting effect emerged from the column before those active principally in the Sayers' test. These findings have led Young[504, 505] to postulate that two pituitary factors influence the adrenal cortex: an adrenal weight factor (AWF) and an ascorbic acid factor (AAF). He has stated that various pituitary extracts have markedly different AAF:AWF ratios. Although Young and his associates have used growth hormone as a convenient source of AWF, they state that they have no reason to believe that the adrenal weight factor is growth hormone itself.[502] The possibility remains that widespread discrepancies exist between the chemical nature of the actual circulating hormone and the highly purified fractions derived from pituitary-gland extracts.

Release of ACTH

It is well established that the release of ACTH from the anterior pituitary gland is an essential element in the mechanism responsible for adrenocortical activation. In man, highly purified preparations of ACTH have been observed to produce all the changes elicited by the administration of crystalline adrenal steroids. In animals exogenous stress increases adrenocortical weight and decreases the concentration of cholesterol, ascorbic acid and sudanophilic material. In the absence of the pituitary gland none of these changes are observed. Furthermore, hypophysectomy results in adrenocortical atrophy,[470] and the hypophysectomized animal, like the adrenalectomized animal, is extremely sensitive to a great variety of nonspecific stresses.[506, 507]

Source of ACTH

There is little agreement concerning the specific cellular source of ACTH in the anterior pituitary gland. Early evidence derived from the study of the hypophysis in patients with Addison's disease suggested that the basophils were the site of secretion.[508] The correlation described by Cushing[509] between the presence of a basophilic pituitary tumor and the existence of clinical manifestations now recognized to be the consequence of adrenocortical hyperfunction has also implicated the basophilic cells as the source of ACTH. D'Angelo et al.[510] noted that starvation in animals was characterized by a decrease in the number of pituitary acidophils, an increase in the number of basophils and adrenal hyperplasia. These findings were interpreted as indicating an increased output of ACTH from the basophils, but the possibility remains that hormones other than ACTH were primarily involved. Finerty

and Briseno-Castrejon[511] observed that in unilaterally adrenalectomized rats with compensatory hypertrophy of the remaining adrenal gland the number of acidophils in the anterior pituitary gland was considerably increased. They therefore postulated that ACTH was derived from the acidophilic cells. Pearse[512] concluded that histochemical technics are inadequate at the present time to identify the source of ACTH. Recently, Marshall[513] prepared fluorescein-tagged antiserums to hog ACTH. Examination under fluorescent light of hog pituitary slices exposed to the tagged antiserums showed that only the basophils stained to any significant degree, suggesting that that cell is the source of ACTH. Although the question cannot be considered settled conclusively, majority opinion favors the origin of ACTH from the basophils.

Regulation of Secretion

An increase in the rate of ACTH release has been assumed to be the mechanism responsible for the increase in adrenocortical secretion observed in a wide variety of situations. Three types of regulatory mechanisms have been considered to control the rate of discharge of ACTH: humoral; sympathicoadrenal; and neurohumoral.

Humoral control. Sayers[192] has suggested that the regulation of the adrenocortical secretion of steroids and the pituitary release of ACTH are controlled by the blood level of adrenocortical hormones. Thus, a fall in the circulating level of adrenocortical steroids as a result of increased cellular utilization serves as a stimulus to augment the secretion of ACTH. Conversely, an abnormally high blood level of corticosteroids inhibits the rate of ACTH release. A considerable body of direct evidence for this hypothesis has been accumulated in both animals and man. The adrenocortical hypertrophy that follows unilateral adrenalectomy appears to represent a compensatory increase in ACTH output as a result of a temporary decrease in the circulating level of adrenocorticosteroids. The prolonged administration of adrenal steroids results in adrenocortical atrophy.[39, 514] Furthermore, the discharge of ACTH in response to exogenous stress may be blocked by the administration of cortical hormones and the amount of steroid required to suppress adrenocorticotrophic activity varies directly with the intensity of the stress.[192] These relations have been considered to demonstrate that the rate of ACTH release from the pituitary gland reflects the varying requirement of the organism for adrenocortical hormones. Sayers and Sayers[194] have suggested that the regulating effect of circulating cortical steroids on ACTH discharge involves a direct effect of the steroids on the hypophysis.

The main obstacle to accepting a mechanism based on reciprocal blood levels of adrenal steroids and ACTH as the sole regulator of ACTH release concerns the rapidity with which the pituitary-adrenal system is capable of responding to certain stimuli. For example, Gray and Munson[515] have shown that after intravenous histamine injection in rats ACTH is discharged within a few seconds. Long[516] has described an equally rapid response to sensory-nerve stimulation. Nevertheless, it appears that the peripheral humoral mechanism of pituitary-adrenal control contributes to the basic regulation of the release of ACTH.

Sympathicoadrenal control. As an extension of the classic view of Cannon[517] concerning the ubiquitous role of the autonomic nervous system and epinephrine in the preservation of homeostasis, Long et al.[518, 519] have postulated that the prompt release of ACTH from the hypophysis under conditions of stress is a result of the secretion of epinephrine. In support of this concept they have reported a delay in the adrenocortical response to stress in the demedullated animal and have demonstrated that the direct application of epinephrine to pituitary transplants in the anterior chamber of the eye results in a significant degree of eosinopenia.[520] Previous studies had demonstrated a satisfactory correlation between eosinopenia and adrenal ascorbic acid depletion after epinephrine. Considerable disagreement exists, however, concerning the capacity of the demedullated or sympathectomized-demedullated animal to respond to stress; most workers[521-523] have reported normal adrenocortical responses in these animals. Vogt[524] found that the intravenous infusion of epinephrine in splanchnicectomized dogs resulted in a prompt rise in the adrenal venous content of substances capable of protecting adrenalectomized animals from cold stress. The effect was attributed[525] to an increase in the rate of ACTH release. However, the specific circumstances under which this response was obtained (splanchnicectomized dogs) should be considered carefully in application of these observations to the intact organism and to other species.

Recent studies in *man* have failed to support the concept of epinephrine as a physiologic activator of the pituitary-adrenal system. Although it is well known that the administration of adequate doses of epinephrine to human subjects produces a significant degree of eosinopenia[522] subsequent investigations have not succeeded in demonstrating that this fall in the number of circulating eosinophils is the result of an increase in the rate of secretion of steroid hormones from the adrenal cortex. After administration of epinephrine an eosinopenia can be elicited in patients with Addison's disease[522] and has frequently been observed to follow complete bilateral adrenalectomy.[3] The administration of epinephrine has resulted in a marked fall in circulating eosinophils even though repeated intravenous infusions of ACTH have produced no effect. Nelson[526] recently found that the blood level of 17-hydroxycorticosteroids in normal subjects and patients did not change after the intravenous injection of epinephrine

despite a fall in blood eosinophils. Jeffries[527] was also unable to produce either metabolic changes or urinary-steroid changes with epinephrine consistent with increased ACTH release. Thorn et al.[3] compared the effects of intravenous, subcutaneous and intramuscular injections of epinephrine in normal subjects with those produced by ACTH. Despite the occurrence of eosinopenia, no rise in the urinary output of 17-hydroxycorticoids was obtained (Fig. 25). Although the administration of extremely large quantities of epinephrine (such as 15 to 30 mg. per day) to patients receiving a sympatholytic agent has been demonstrated to result in an increase in urinary 17-ketosteroids,[528] the doses of epinephrine required to produce this effect can hardly be considered physiologic.

It must be concluded that with the methods presently available it has not been possible to demonstrate an elevation in the rate of adrenocortical steroid secretion in *man* with reasonable doses of epinephrine; furthermore, epinephrine has been shown to produce eosinopenia in the absence of functioning adrenocortical tissue. Although the fall in circulating eosinophils that occurs after ACTH administration has been found to be closely correlated with the rise in urinary 17-hydroxycorticoids,[3] it is evident that eosinopenia alone does not provide a reliable index of adrenocortical activation after either the administration of epinephrine or exposure of the patient to environmental conditions capable of stimulating the release of epinephrine or other eosinopenic agents.

Neurohumoral control. There is a growing body of evidence that the secretory functions of the anterior pituitary gland are significantly influenced by the hypothalamus. In view of the established importance of hypothalamic centers in the regulation of the activities of the autonomic nervous system, it is evident that the hypothalamus occupies a strategic position for the integration of the adaptive and regulatory functions of the endocrine system and vegetative nervous system. Definitive evidence for the stimulation of ACTH discharge by the hypothalamus has been derived from the experiments of Harris[529, 530] and Hume.[531, 531] These investigators have shown that strategically placed lesions in the hypothalamus of both rabbits and dogs can abolish the pituitary-adrenal response to exogenous stress and, conversely, utilizing remote control stimulation of implanted coils as described by Harris,[532] that electric stimulation of carefully localized areas of hypothalamus produces a lymphopenia and eosinopenia interpreted as indicating adrenocortical stimulation consequent to the discharge of ACTH from the anterior pituitary gland. Stimulation of the gland itself was quite ineffective in eliciting an adrenocortical response.

Results obtained by various workers on the effect of stalk section on anterior pituitary function have been highly variable. The work of Popa and Fielding[533] in 1930 demonstrated that the collection of blood vessels that courses along the pituitary stalk is actually a portal system. Subsequently, Wislocki[534] and others[535, 536] established the direction of flow in this portal system as being from the capillary plexus of the median eminence to the sinusoids of the pars distalis. The careful work of Harris[532] has demonstrated the importance of this vascular bed to the normal function of the anterior pituitary gland. It now appears that pituitary-stalk section may interfere with the secretory function of the pars distalis, provided regeneration of the portal system is successfully prevented. Con-

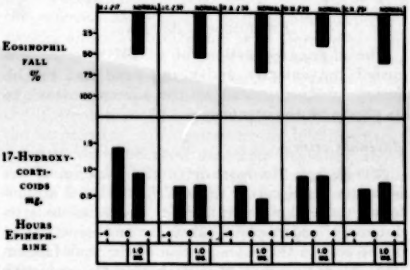

FIGURE 25. *Eosinophil and 17-Hydroxycorticoid Responses to Intravenous Infusion of Epinephrine.*

17-hydroxycorticoids were measured on four-hour urine samples collected before and during epinephrine administration. Eosinophils were counted at the beginning and completion of epinephrine infusion.

firmatory evidence for this has been derived by Harris and Jacobsohn[537] from the study of functional hypophyseal grafts. Hypophyseal tissue was grafted into hypophysectomized rats in two locations: beneath the temporal lobe of the brain and beneath the median eminence of the tuber cinereum. Adequate revascularization of the latter grafts from the hypophyseal portal system was demonstrated. Histologic study showed that grafts beneath the temporal lobe exhibited an abnormal chromophobe to chromophil cellular ratio despite apparently normal vascularization, whereas grafts beneath the median eminence presented a normal pattern of cellular differentiation. Animals possessing subtemporal grafts showed a definite lack of gonadotrophic and growth-hormone activity, and the adrenal glands in these animals were moderately atrophic. In contrast, animals with grafts beneath the median eminence exhibited normal reproductive function, and histologic examination of the ovaries and adrenal and thyroid glands revealed a normal structure. However, Cheng et al.[538] and Fortier[539] have shown that hypophyseal transplants in the anterior chamber of the eye are capable of discharging ACTH in response to acute stress despite ab-

normalities of cellular differentiation in the transplanted tissue. The former utilized reduction in adrenal ascorbic acid content as an indication of ACTH release, whereas the latter employed the eosinophil response.

On the basis of the evidence cited above, it may be postulated that the release of ACTH by the anterior pituitary gland is subject to hypothalamic control through a humoral mechanism mediated directly through the hypophyseal portal vascular bed and indirectly, especially during conditions of stress, through the systemic circulation. It is to be emphasized, however, that the ultimate proof of such a mechanism awaits the actual demonstration of an increase in the circulating level of ACTH.

Physiologic Actions

The physiologic actions of ACTH may be discussed conveniently under two headings: the influence of this hormone on the adrenal cortex and its effects on the organism.

Adrenal Cortex

Morphology. In a study of the response of the human adrenal cortex to ACTH O'Donnell et al.[192] found the earliest morphologic changes to be a reduction of sudanophilic substance and hypertrophy of the cells in the outer portion of the zona fasciculata. More prolonged stimulation led to a reduction of lipids in all areas of the cortex and further hypertrophy, which was particularly marked in the cells of the fascicular and reticular zones. At this stage the zona glomerulosa was ill defined, in general less than normal in width and many of its cells were hypertrophied. The changes in this zone were considered the result of a transformation of glomerulosa cells to cells of the fasciculate and reticular layers, a phenomenon that has been reported in animals.[540]

Landing and Feriozi,[541] studying the morphology of the adrenal glands of 9 children with acute leukemia and 1 child with the nephrotic syndrome who died during ACTH therapy, found that in the former the weight of the adrenal glands was above normal, the cells of the fasciculate and reticular zones were larger than normal and their fat content was decreased. The zona glomerulosa showed no apparent change. In the patient with nephrosis, however, there was an increase in zone thickness and cell size with a decrease in fat in all three zones of the adrenal cortex.

It thus appears that in man, although the morphologic response of the zona glomerulosa to ACTH may be slight when compared to that of the fascicular and reticular zones, the entire adrenal cortex is sensitive to ACTH stimulation. This is apparently true also in both the mouse[542] and the dog.[543] In the rat, however, the zona glomerulosa seems to be relatively independent of pituitary control, as indicated by its failure to show involutionary changes after hypophysectomy[544] or administration of cortisone[191, 209] and by its failure to reveal proliferatory or secretory changes after the administration of ACTH.[193]

Chemistry.

Ascorbic acid: Investigations of the changes in adrenal ascorbic acid under a variety of experimental conditions have been ably reviewed by Sayers and Sayers.[193] In general, increased adrenocortical activity is associated with a reduction in the concentration of adrenal ascorbic acid. Administration of ACTH leads to a rapid depletion of adrenal ascorbic acid in the guinea pig and the rat.[545] In rats the concentration of ascorbic acid falls appreciably within twenty minutes of injection of the hormone, decrease being maximal at one hour, but within three hours, the concentration has begun to rise and in nine to twelve hours has returned to normal; with repeated administration of ACTH the adrenal ascorbic acid remains at a low level, but this is only temporary, for with prolonged stimulation by the trophic hormone the concentration of ascorbic acid in the adrenal cortex gradually returns to normal.

The part played by ascorbic acid in the metabolic processes of the adrenal cortex is unknown. Lowenstein and Zwemer[546] reported the isolation and characterization of a water-soluble conjugate of a cortical steroid and ascorbic acid. This finding has not, however, been confirmed. A number of observations suggest that ascorbic acid does not play an essential role in the functional activity of the adrenal cortex. Impairment of liver glycogen deposition in scorbutic animals, a defect in carbohydrate metabolism characteristic of scurvy, is not improved by adrenocortical extract.[547] Patients with scurvy excrete corticoids at a normal rate.[548] Finally, ACTH produces a normal fall in adrenal cholesterol content, together with a lymphopenia, in guinea pigs in which a scorbutic diet has virtually eliminated the concentration of ascorbic acid in the adrenal gland.[549]

Little is known of the effect of ACTH on the content of ascorbic acid in the human adrenal cortex. Beck et al.[550] observed an initial rise in blood and urinary ascorbic acid in patients receiving ACTH. With continuing stimulation, however, the elevated blood and urinary levels returned to normal. These authors suggested that their findings indicated a rapid release and synthesis of ascorbic acid by the adrenal cortex in response to ACTH.

Cholesterol: Cholesterol is present in high concentration in the adrenal cortex. When the gland is relatively inactive approximately 5 per cent of the wet weight of the tissue is cholesterol, a concentration higher than that found in any other tissue, including brain.

The relation of adrenal cholesterol content to the secretory activity of the adrenal cortex has been reviewed by Sayers et al.[478] Situations that increase

adrenocortical secretion are associated with a reduction in the concentration of cholesterol in the adrenal gland. ACTH administration results in a depletion of the adrenal cholesterol in animals[475] and man[551] at a time when metabolic changes characteristic of adrenocortical hyperactivity are occurring in the organism. In the absence of the anterior pituitary gland, adrenal cholesterol content does not change in response to stress and is usually fixed at a concentration higher than normal.[552] These findings, together with the observation that ACTH enhances the transformation of cholesterol to corticoids in the perfused bovine adrenal gland,[4] leave little doubt that the fall in adrenal cholesterol concentration with ACTH indicates that the sterol is serving as a corticoid precursor.

Alpha-ketolic corticoids: It is well known that the administration of ACTH to man is followed by an increased excretion of alpha-ketolic corticoids (formaldehydogenic steroids or reducing corticosteroids) in the urine (Fig. 19). These consist largely of tetrahydrocortisone, tetrahydrohydrocortisone, hydrocortisone and cortisone.[411] That these urinary changes reflect an increased synthesis, as well as an increased secretion, of alphaketolic corticoids from the adrenal gland is evident from studies with the isolated adrenal gland[4] and adrenal slices.[553] Hechter and his co-workers[4] showed that when ACTH was added to blood that was being perfused through bovine adrenal glands, the resulting increase in alpha-ketols in the perfusate could not be explained by the small decrease in the corticoid content of the gland. Furthermore, Haynes et al.[553] observed that ACTH enhanced the incorporation of C_{14} from radioactive acetate into hydrocortisone in the presence of beef adrenal slices.

There is strong evidence that the principal alpha-ketolic corticoids secreted by the adrenal cortex in response to ACTH are hydrocortisone and corticosterone. Of the 15 steroid ketols detected in ACTH perfusates of bovine adrenal glands, hydrocortisone and corticosterone were present in the greatest concentration, representing together approximately 60 per cent of the total alpha-ketolic corticoids. 11-dehydrocorticosterone (Compound A), cortisone and 11-desoxycorticosterone were also detected in these perfusates.[4] The remaining 10 compounds have not been identified although a number appear to be reduction products of the known corticoids. Hydrocortisone and corticosterone have also been isolated from the adrenal venous blood of dogs after ACTH stimulation[391, 394] and from dialysates of the peripheral blood of dogs.[392]

The manner in which ACTH stimulates the synthesis of alpha-ketolic corticoids by the adrenal cortex is not clear. It is known that the trophic hormone enhances the synthesis of hydrocortisone from both cholesterol and acetate in the perfused adrenal gland[4] and from acetate by adrenocortical slices.[553] Of the intermediate reactions involved in this synthesis, three have been more or less clearly delineated: hydroxylation at carbon-11 has been demonstrated in perfused adrenal glands,[4] in adrenal homogenates[482, 554, 555] and in mitochondrial fractions of the adrenal cortex[556] with both desoxycorticosterone and 11-desoxy-17-hydroxycorticosterone (corticosterone and hydrocortisone, respectively, were the products formed); hydroxylation at carbon-21 has been shown to occur in perfused adrenal glands[4] and adrenal homogenates[554] with progesterone, 17-hydroxyprogesterone, and 21-desoxycortisone as substrates (the products obtained were corticosterone, hydrocortisone and cortisone, respectively); and hydroxylation at carbon-17 has been effected in the perfused adrenal gland with progesterone as substrate (both 17-hydroxyprogesterone and hydrocortisone were formed[4]). The observation that in the perfused adrenal gland ACTH does not *enhance* either the transformation of desoxycorticosterone and 17-hydroxy-11-desoxycorticosterone to 11-oxygenated corticosteroids or the conversion of progesterone to hydrocortisone suggests that the three reactions described above are uninfluenced by the trophic hormone. This finding led Hechter et al.[4] to postulate that the stimulatory effect of ACTH on the synthesis of hydrocortisone and corticosterone occurs at some stage before the formation of progesterone, and they have suggested that ACTH may control the degradation of the cholesterol side-chain by an adrenocortical enzyme system.

While it is still uncertain that desoxycorticosterone is a natural secretory product of the adrenal cortex, it appears likely that more potent electrolyte-regulating compounds than hydrocortisone and corticosterone are liberated by the adrenal gland. The detection by Simpson et al.[5] of a highly potent substance in adrenal-gland extracts and in the adrenal venous blood of animals tends to support this view. This substance is distinct from hydrocortisone, cortisone and corticosterone and is much more highly potent in its salt-retaining capacity than any of these compounds.

17-Ketosteroids: It is well known that the administration of ACTH to man leads to an increased excretion of 17-ketosteroids in the urine. Dobriner and his co-workers[411, 557] have shown that there is an increase both in 17-ketosteroids with an 11-oxygen group (for example, 11-hydroxyandrosterone, 11-hydroxyetiocholanolone and 11-keto-etiocholanolone) and in those lacking an oxygen atom at carbon-11, such as androsterone and etiocholanolone. The administration of cortisone to man, on the other hand, results in an increase only in 11-oxygenated 17-ketosteroids. It is believed that the adrenal precursors of the 11-desoxy 17-ketosteroids may be hormones that, unlike cortisone, hydrocortisone and corticosterone, do not possess an oxygen atom in the 11 position — for example, 11-desoxy 17-hydroxycorticosterone (Compound S) and 17-

hydroxyprogesterone. This belief is supported by the demonstration that the administration of such substances labeled with radioactive carbon leads to the excretion in the urine of radioactive androsterone and etiocholanolone.[411] Furthermore, the administration of large doses (300 mg. per day) of hydrocortisone, cortisone and corticosterone to patients who had undergone orchiectomy and bilateral adrenalectomy for metastatic carcinoma of the prostate did not raise the level of urinary biologically active androgens above that of a castrated male.[412] Finally, it is of interest that Gassner et al.[558] have reported the isolation of a fraction that possessed androgenic activity and gave the reaction for 17-ketosteroids from the adrenal venous blood of cows that had been given ACTH. These findings make it seem improbable that hydrocortisone is the sole steroid secreted by the adrenal cortex as proposed by Conn et al.[440]

The 17-ketosteroid, dehydroisoandrosterone, has long been considered to be of adrenal origin. This is based on its isolation from the urine of castrate men[559] and from the urine of normal[560] and castrate women.[561] It has been found in large amounts in the urine of patients with adrenal tumors.[562] Furthermore, it has not been demonstrated to be a metabolite of testosterone.[563] Recently, Landau et al.[563] and Wolfson and his associates[78] have observed increases in the Pettenkoffer chromogen in the ketonic fraction of the urine of patients receiving ACTH. Under similar circumstances, Ronzoni[564] has reported an increase in the color given by the Allen reaction.[565] Although these reactions are given by dehydroisoandrosterone, doubts about their specificity for dehydroisoandrosterone alone[566, 567] make it uncertain at present whether ACTH induces the adrenal cortex to secrete this steroid or its precursor.

Estrogens: In 1939 Beall[568] reported the isolation of estrone from ox adrenal glands. Excessive quantities of estrogens, as determined by bioassay, have been detected in the urine of certain patients with adrenal tumors.[569, 570] From the urine of 1 such subject, Mason and Kepler[571] were able to isolate estrone. After ACTH administration, Nathanson et al.[572] observed rises in urinary estrone, estradiol and estriol in 3 female patients but not in 2 male subjects studied. One of the female patients was subsequently found to have atrophic ovaries, and it was believed that the origin of the estrogens must have been the adrenal cortex. Paschkis,[572] using a bioassay method, noted rises in estrogen excretion in the urine of 2 male patients after ACTH stimulation. These observations suggest that estrogens or estrogen precursors may be liberated by the adrenal cortex in response to ACTH.

Progesterone: Progesterone was first isolated from ox adrenal glands in 1938 by Beall and Reichstein.[574] Its urinary excretory product, pregnandiol, has been found in increased amounts after the intramuscular administration of desoxycorticosterone to man.[40] Dobriner et al.[411] have noted an increased excretion of pregnanolone, a probable reduction product of progesterone, in the urine of patients after ACTH stimulation, but not after the administration of cortisone. Recently, an increased excretion of pregnandiol-like substances has been observed in man after major surgical procedures and the administration of ACTH, but not cortisone.[575] It seems probable from these observations that progesterone or a precursor of this compound is released by the adrenal cortex in response to ACTH.

In summary, it appears that ACTH stimulates the synthesis, as well as the release, of steroids from the adrenal cortex. Hydrocortisone and corticosterone are the major corticoids liberated. It seems, however, that electrolyte-regulating compounds more highly potent than these substances are released in response to ACTH. In addition there is strong evidence that androgens or androgen precursors other than hydrocortisone or corticosterone are produced by the adrenal cortex. Finally, there is evidence that estrogens and progesterone or precursors of these compounds may be secreted by the adrenal gland after ACTH stimulation.

The Organism

Effects mediated by the adrenal cortex. In general, except in cases in which the adrenal cortex is unable to respond or ACTH "resistance" has developed, the biologic effects of ACTH are qualitatively similar to those of cortisone and hydrocortisone. The actions of cortisone and hydrocortisone have been presented in some detail. Only the effects of ACTH that differ appreciably from those of the two corticoids are discussed.

In short-term experiments (six to nine days) in man, Conn et al.[576] and Perera and his associates[577] observed that cortisone had little or no effect on the level of serum cholesterol. With prolonged cortisone administration, however, Adlersberg, Schaefer and Drachman[578] noted that the total serum cholesterol frequently increased, with a concomitant rise in cholesterol esters. In contrast, in short-term studies with ACTH there was a precipitous fall in total serum cholesterol on the third to the fifth day after the institution of therapy; this decrease was mainly at the expense of the ester fraction.[576] In Addisonian patients no change in the concentration of serum cholesterol followed ACTH administration. Conn et al.[576] postulated that the serum cholesterol, particularly the ester fraction, might serve as a precursor in the synthesis of adrenocortical hormones after the adrenal cortex has been depleted of its reserve supply of cholesterol during stimulation by ACTH. With prolonged administration of ACTH, however, Adlersberg, Schaefer and Drachman[578] observed a gradual rise in serum cholesterol concentration that was largely due to an increase in the concentration of cholesterol esters. Wolfson and his associates[201] suggested that the

elevation in serum cholesterol seen with both cortisone and ACTH therapy was in part a manifestation of a depression of thyroid function.

A major, but as yet unsolved, problem is the interpretation, in terms of the corticoids responsible, of the pronounced sodium and chloride retention that follows ACTH administration. Although the exact status of desoxycorticosterone as a natural mineralocorticoid is still uncertain, the recent isolation of a highly potent electrolyte-regulating compound from the adrenal venous blood of animals[5] suggests that ACTH might stimulate the adrenal cortex to release a specific salt-retaining substance in addition to the glucocorticoids. On the other hand, whereas it was originally thought that the secretion of cortisone and hydrocortisone alone from the adrenal cortex could not account for the degree of sodium and chloride retention observed after the administration of ACTH, recent studies[3] have shown that the intravenous infusion of cortisone or hydrocortisone at a rate of 12 mg. per hour can result in the virtual extinction of sodium from the urine of human subjects. Thus, the salt retention that follows ACTH administration can conceivably be explained on the basis of an increased secretion of cortisone or hydrocortisone. Finally, it is possible that corticoids such as corticosterone (Compound B) and dehydrocorticosterone (Compound A), which are known to be more potent in electrolyte regulation than the 11,17-oxysteroids, contribute to a considerable degree to the over-all effect of sodium and chloride retention of ACTH.

Changes in the anterior pituitary gland have been observed in patients receiving long-continued ACTH treatment. An increase in the number of basophils, with the development of Crooke's hyaline cytoplasmic changes, and basophilic stippling of many of the chromophobe cells were observed by Golden et al.[579] in the anterior pituitary glands of 2 patients. Similar findings were obtained by Laqueur.[550] Landing and Feriozi[541] described an increase in size and degranulation of the pituitary basophils of leukemic children who died while being treated with ACTH. After withdrawal of ACTH, clinical evidence of adrenal insufficiency, as indicated by weakness, fatigability, hypotension and collapse, may appear. These signs and symptoms may be accompanied by a relatively high eosinophil count and a relatively low 17-ketosteroid and formaldehydogenic steroid excretion in the urine. It is probable that the increased corticoid secretion induced by exogenous ACTH depresses the output of ACTH by the pituitary gland in the same manner as administered cortisone.

The effects of ACTH and cortisone on the integumentary system are virtually identical. ACTH is, of course, not effective when applied locally. There does appear to be a difference between the two hormones in their effect on skin pigmentation. In studies of patients with Addison's disease McCracken and Hall,[581] using reflectance spectrophotometry, observed that cortisone led to a decrease in skin pigmentation that was largely due to a diminished melanin content. In patients with intact adrenal glands, on the other hand, the administration of ACTH resulted in an increased melanin content of the skin; this may be correlated with the observation that darkening of the skin in man frequently occurs during ACTH therapy. It has been suggested that contamination of ACTH by intermedin (melanophore-expanding hormone) is responsible for this phenomenon[191] although an influence of intermedin on melanin in mammalian skin has yet to be clearly demonstrated.

Whereas there appears to be little difference between ACTH and cortisone in their effects on the electroencephalogram and psyche in man, Woodbury[146] has demonstrated a difference in their influence on the electroshock seizure threshold (EST) in rats. Cortisone produced a marked and ACTH a slight increase in EST.

Extra-adrenal actions. Two types of extra-adrenal actions of ACTH have been described. One appears to involve the mediation of adrenal steroids in pregnancy. This action is considered to be an effect of ACTH on placental production of corticosteroids. In this regard, Jailer[582] has observed a normal eosinophil response to ACTH in 2 patients with Addison's disease during pregnancy but not during the post-partum period. Since it is known that the steroid level in the urine of newborn infants is extremely low, it appears unlikely that the fetal adrenal gland is responsible for this change. It is of interest, in this connection, that cortisone and hydrocortisone have recently been isolated from human placental tissue.[393]

The second type of extra-adrenal action of ACTH envisages a biologic effect of ACTH not mediated by adrenocortical steroids. A number of studies in animals have been reported in which effects of ACTH preparations have been observed in the absence of the adrenal cortex.[583-585] It remains to be established whether the effects observed to date are the result of an extra-adrenal action of ACTH or of contaminating pituitary substances. To date, no action of ACTH not mediated by adrenocortical steroids has been demonstrated in man.

Metabolic Fate of ACTH

Information on the metabolism and excretion of ACTH is meager. Sayers and his co-workers[586] have shown that ACTH disappears rapidly from the circulation after intravenous administration. When normal human subjects were given 50 to 100 international units of the hormone in thirty minutes to an hour by the intravenous route it was found that the elevated plasma ACTH levels returned to normal within two hours of completion of the infusion. Greenspan, Li and Evans[587] reported more rapid disappearance of ACTH after intra-

venous injection into rats. The level of plasma ACTH fell in a logarithmic fashion, and the half life of the injected ACTH activity was found to be five and a half minutes. In addition, it was observed that the initial plasma concentration of the hormone immediately after injection was only 6 per cent of the theoretically expected level. The disappearance of ACTH from the circulation may be due to one or more of the following factors: inactivation or catabolism, distribution and tissue fixation, or excretion. A rapid inactivation of ACTH in vitro has been reported by Pincus et al.[588] When highly purified preparations were incubated with rat or human blood, 40 to 70 per cent of the corticotrophic activity was lost within an hour. Evidence was obtained that suggested the presence of an inactivating system consisting of a heat-labile and heat-stable substance. There is little doubt that circulating ACTH is rapidly fixed by certain tissues. Sonenberg and his associates[589] observed a rapid, but short-lived, deposition of radioactivity in the adrenal cortex of rats that had received intracardiac injections of I^{131}-labeled preparations of ACTH. Radioautographs showed the radioactivity to be particularly concentrated in the inner layers of the cortical tissue. Richards and Sayers[590] studied the fate of intravenously injected ACTH in normal rats. Five minutes after injection 40 per cent of the administered hormone was in the extracellular fluid, and 20 per cent was fixed in the kidneys. At fifteen minutes a negligible amount of ACTH was found in the extracellular fluid, whereas 15 per cent remained in the kidneys. A small quantity of ACTH was detected in the adrenal glands, but none in the liver or urine.

Toxicity

Effects of Stimulation of the Adrenal Cortex

Prolonged administration of ACTH, with resultant intense adrenocortical hyperactivity, may eventually lead to the appearance of the same undesirable effects that are seen with long-continued cortisone therapy (discussed in the previous section on cortisone). As with cortisone, these effects are of two types: those due to overdosage of the hormone that occur during its administration and consist of one or more of the manifestations of Cushing's syndrome; and those that follow hormone withdrawal and reflect a state of adrenal insufficiency induced by pituitary inhibition. The appearance of the former effects is influenced to a considerable degree by the mode of administration of ACTH. When the hormone is given by intramuscular injection a more sustained action is achieved than that which occurs when ACTH is administered in a daily eight-hour intravenous infusion. Consequently, when patients are treated by the latter method overdosage phenomena are usually less marked and less frequent. Although the overdosage effects of ACTH and cortisone are qualitatively similar, certain quantitative differences exist. At a given level of therapeutic effectiveness edema from sodium and water retention and evidence of increased androgen secretion — acne and hirsutism — are often more prominent during treatment with ACTH than with cortisone. The former may well reflect the adrenocortical secretion of steroids more potent in electrolyte regulation than cortisone, and the latter the direct secretion of androgenic substances.

Symptoms of adrenal insufficiency that may appear upon cessation of ACTH treatment may be mild or severe, depending on the duration of therapy, level of hormone dosage and rapidity of hormone withdrawal. Extreme care should be exercised in withdrawal of the hormone, particularly after a prolonged period of therapy. ACTH dosage should be tapered slowly with a gradual increase in the interval between doses until normal levels of endogenous adrenocortical secretion are restored and maintained. In general, the duration of relative adrenal insufficiency after the termination of a long period of ACTH therapy is less prolonged than that which follows long-continued treatment with cortisone.

Effects of the ACTH Preparation Itself

There is a possibility that large doses of ACTH over long periods will in some way injure or exhaust the human adrenal cortex through "overstimulation." The observations of Ingle,[591] who found hemorrhages in the adrenal cortexes of rats after intensive ACTH stimulation, were partly responsible for such fears, which, fortunately, have not been realized. Even *maximal* adrenocortical stimulation by the continuous intravenous infusion of ACTH over periods as long as ten days has given no evidence of permanent alterations in adrenal function in man.

Earlier ACTH preparations frequently contained sufficient quantities of posterior pituitary hormones to cause overt pressor and antidiuretic effects. With improved methods of purification these substances have largely been eliminated from the commercial preparations of ACTH now available.

Sensitivity reactions to ACTH itself or to some factor in the preparation have occasionally been reported. These reactions have been of two main types. The *immediate* reaction has appeared within a few minutes of intramuscular injection or the initiation of an intravenous infusion of the hormone. Its manifestations have been itching and urticaria, occasionally wheezing and angioneurotic edema, and very rarely anaphylactic shock.[592, 593] The *delayed* reaction begins several hours after the institution of ACTH therapy, by either the intramuscular or the intravenous route, and consists of fever and malaise.[592] These reactions have become rare now that the purity of the commercial ACTH preparations has been improved. It should

be emphasized, however, that patients who have undergone bilateral adrenalectomy or who have Addison's disease or panhypopituitarism are much more likely to react adversely to ACTH preparations. This is particularly true if the hormone is being given by intravenous infusion.[482] It appears that a responsive adrenal cortex will protect the patient to a considerable degree against a sensitivity reaction. Consequently, in patients with adrenal insufficiency caution should be exercised when intravenous infusions of ACTH are given. During the course of several thousand intravenous infusions of ACTH we have encountered only 6 potentially serious untoward reactions. Delayed, febrile reactions have occurred in 2 patients with Addison's disease. Urticaria and pruritus have occurred almost immediately after the start of intravenous infusions of ACTH in 3 patients with Addison's disease and in 1 patient after the termination of a prolonged course of cortisone therapy. All the patients involved had received ACTH on previous occasions. It should be noted that in 3 of these patients repeated intravenous infusions of a highly purified, potent preparation of ACTH were administered without any reactions. It therefore appears probable that reactions of this type are produced by inert protein rather than by ACTH itself.

Preparations and Routes of Administration

As a consequence of the extensive research devoted to the isolation of ACTH remarkably potent and highly purified preparations of the hormone are now available. It should be emphasized that both the purification and large-scale production of ACTH have been greatly facilitated by the adrenal ascorbic acid depletion method of ACTH bioassay developed by Sayers and his associates[479] in 1948. This procedure has served as the basis of standardization of both the international and *U.S.P.* ACTH standards.

The majority of commercial preparations of ACTH are derived from either hog or sheep pituitary glands. Potent preparations have also been obtained from beef pituitary glands, and it is of interest to note the successful use of whale pituitary glands as a source of corticotrophin in Norway.[504] At present most preparations are remarkably free of contaminating pituitary hormones — luteotrophin, thyrotrophin and posterior pituitary factors.

Two types of ACTH preparations are now available for therapeutic use: a standard, short-acting preparation, available either as a lyophilized powder or as a stable solution in water containing 1 per cent phenol, for subcutaneous, intramuscular or intravenous use; and a long-acting preparation of lyophilized ACTH incorporated in a gelatin menstruum for subcutaneous or intramuscular injection.

Short-Acting Preparations

Powdered preparations are dissolved in physiologic saline solution or distilled water immediately before injection. Since the metabolic effects of a single injection of these preparations are comparatively brief, administration must be repeated at intervals of six to eight hours to achieve continuing adrenocortical stimulation. The eosinopenia produced by the intramuscular injection of a single dose of 25 *U.S.P.* units of a lyophilized preparation of ACTH is maximal four to six hours after injection. The eosinophil level usually returns to normal after eight to twelve hours.

Since the intensity of adrenocortical response elicited in different persons may vary significantly, no fixed dosage schedules can be prescribed. In general, an effective therapeutic response can ordinarily be produced at a total daily dosage level of 40 to 80 units, administered in divided doses at intervals of six or eight hours. In some cases, however, much higher dosages (such as 200 units daily) may be required during the initial period of therapy. At continuing dosage levels of 100 units per day or above, undesirable physiologic or metabolic effects frequently appear. Once a satisfactory clinical remission has been obtained, the total daily dosage of ACTH should be reduced to the minimal level consistent with the maintenance of a satisfactory therapeutic response. For example, individual doses may be reduced by 5 units daily, at intervals of three to five days, until a satisfactory maintenance schedule is established. Subsequently, the interval between doses may be lengthened, but unfortunately the majority of patients continue to require two or three doses of regular ACTH a day to achieve an effective maintenance level of adrenocortical stimulation.

In the past a number of patients treated with ACTH have exhibited increasing unresponsiveness to the hormone administered by intramuscular injection. This phenomenon has been termed "ACTH-resistance"[505] and appears to be the result of intramuscular inactivation or destruction of the hormone since administration of the same preparation by intravenous infusion to these patients produced a normal adrenocortical response. However, certain highly purified preparations of ACTH, such as that described by Astwood,[500] have proved far less susceptible to inactivation. Consequently, the dosage of these preparations required to produce a given level of metabolic and therapeutic activity is approximately a third of that of some widely used types of ACTH prepared by older methods. Despite this significant differential of effectiveness after intramuscular administration, both types of preparation are equally active when infused intravenously. Furthermore, since both types are assayed by the Sayers test, which employs the intravenous route of ACTH administration, it is apparent that a wide discrepancy between the labeled potency and the clinical effectiveness of the two preparations may be demonstrated when they are given intramuscularly. It should be empha-

sized, therefore, that the labeled potency of hormonal preparations will be valid, in general, only when the route of administration employed in assaying a preparation corresponds to the route by which the hormone is given therapeutically.[596] Fortunately, at present the most extensively used preparations of ACTH are so carefully prepared as to be

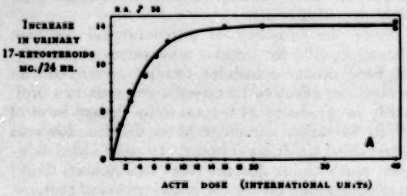

FIGURE 26. *Dose-Response Curve of 17-Ketosteroid Excretion to Increasing Amounts of ACTH Administered Intravenously to a Normal Subject over a Period of Eight Hours.*

almost equally potent by both the intramuscular and intravenous routes, and the problem of ACTH resistance is of far less significance than formerly.

The intravenous route in man was first employed by Sayers et al.,[596] who demonstrated most of the known physiologic effects of ACTH in 2 normal

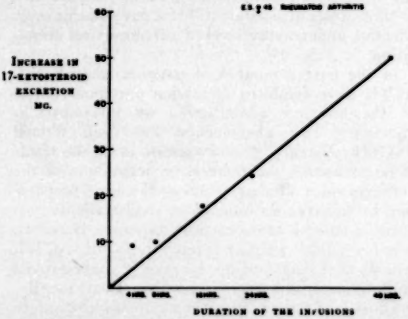

FIGURE 27. *Time-Response Curve of 17-Ketosteroid Excretion to ACTH Infused Intravenously at a Constant Dosage of 20 Units.*

The rises in 17-ketosteroid excretion are expressed as mg. per twenty-four hours except for the forty-eight-hour infusion, which is mg. per forty-eight hours.

subjects after intravenous infusion during a thirty-minute period of comparatively large doses of the hormone. Gordon[597] subsequently demonstrated the therapeutic effectiveness of intravenously infused ACTH in man using continuous infusions extending over several hours or days. Subsequent studies[595, 598] have established the intravenous administration of ACTH as a highly effective and economical method of producing adrenocortical activation. An eight-hour infusion of 20 to 25 *U.S.P.* units has been found to have metabolic and therapeutic effects comparable to those achieved by the daily intramuscular injection of from 100 to 150 units of lyophilized ACTH (35 to 50 units of the highly purified preparations).

Detailed investigations of the intravenous route have delineated the pharmacologic parameters of this method of hormone administration and clarified the physiologic and quantitative aspects of adrenocortical activation.[595] By means of changes in the number of circulating eosinophils and the rise in urinary 17-ketosteroid excretion as indexes of the degree of adrenocortical stimulation obtained, it was demonstrated that the intensity of response

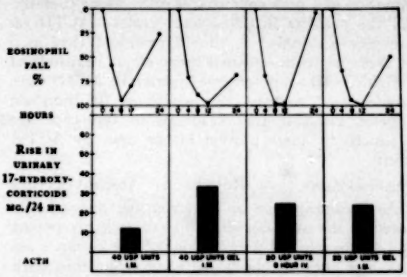

FIGURE 28. *A Comparison of the Results of Administration of Various ACTH Preparations to a Normal Thirty-Two-Year-Old Man.*

produced increased with the amount of ACTH infused up to a critical dosage, over and above which little or no additional response was elicited (Fig. 26). In subjects with normal adrenocortical function, this critical dosage level was approximately 20 units of ACTH infused over an eight-hour period. With a constant dose of 20 units, it was demonstrated that an extension of the period of infusion from thirty seconds to forty-eight hours resulted in a linear increase in the intensity of adrenocortical activation (Fig. 27). It is therefore clear that there is a maximal quantity of ACTH that during a given period of time can be effective in stimulating the adrenal cortex and that the total output of adrenocortical steroids initiated by a standard dose of ACTH varies directly with the duration of the intravenous infusion.

Long-Acting Preparations

To increase the duration of adrenocortical stimulation, the hormone has been incorporated in a gelatin menstruum. Long-acting preparations of ACTH

may be administered subcutaneously or intramuscularly. The ACTH-gel preparations available consist of highly purified hormone prepared by modifications of the oxycellulose column method of Astwood.[600] To date, we have encountered no cases of resistance to these preparations.

Since the intensity of adrenocortical stimulation induced by ACTH has been shown to be a direct function of the duration of continued stimulation of the gland, it was anticipated that the gel preparations would result in enhanced therapeutic effectiveness. That the physiologic and therapeutic effects of a single injection of ACTH in gelatin considerably exceed those resulting from a single injection of an equivalent dose of the lyophilized material is demonstrated in Figure 28. The blood eosinophil and urinary 17-hydroxycorticoid responses produced by the injection of 40 *U. S. P.* units of the same lyophilized preparation of ACTH, in 1 case administered in saline solution and in another dissolved in a 16 per cent gelatin vehicle, are shown. Because of their enhanced adrenocorticotrophic activity, owing to the use of highly purified ACTH as well as to the prolonged period of action, presently available ACTH gels have arbitrarily been restandardized in terms of "clinical" or commercial units rather than *U. S. P.* units. Thus, to elicit a therapeutic effect equivalent to that produced by the intermittent intramuscular injection of 40 *U. S. P.* units per day of older lyophilized preparations of ACTH, a total daily dosage of approximately 14 *U. S. P.* units of the highly purified ACTH in gelatin is ordinarily required. The latter preparation, however, is actually labeled 40 commercial units or as "clinically equivalent to 40 *U. S. P.* units." The gel preparations are therefore labeled in terms of the clinical effect obtained rather than in terms of the actual number of *U. S. P.* units of ACTH contained in the vial. Indeed, the difference in the actual quantity of purified ACTH present can be easily demonstrated by comparing the intensity of adrenocortical stimulation produced by the intramuscular injection of 40 *U. S. P.* units of purified ACTH in gelatin and 40 *clinical* units of an identical preparation; the intensity of adrenal activation elicited by the preparation calibrated on the basis of the *U. S. P.* standard is at least twice as great as that calibrated in terms of clinical equivalents. In summary, highly purified preparations of ACTH injected extravascularly in a gelatin menstruum exert a metabolic and therapeutic effect approximately three times as great as that of an equivalent quantity of the older, less pure, lyophilized preparations of the hormone injected intramuscularly in divided doses.

The intramuscular or subcutaneous injection of approximately 40 clinical or commercial units of ACTH gel elicits an adrenocortical activation approximately equal to that produced by the intravenous infusion of 20 *U. S. P.* units of lyophilized ACTH over an eight-hour period (Fig. 28). The administration of 80 to 120 clinical units in gelatin, results in approximately the same degree of adrenocortical stimulation produced by the continuous twenty-four-hour infusion of 20 to 40 *U. S. P.* units of lyophilized ACTH. The maximal effect of a single dose of ACTH gel, 20 to 40 units, occurs from fifteen to eighteen hours after injection. The total duration of effect, however, extends into the succeeding twenty-four-hour period. It is therefore apparent that the administration of these amounts of ACTH gel in a single daily injection has a continuous effect on the adrenal cortex. For this reason overdosage effects are far more likely to occur during a prolonged course of ACTH gel administration than during the daily eight-hour administration of intravenous infusions. Similarly, the margin between an optimal dose of the gel and a dose capable of producing a significant degree of undesirable side effects may be quite narrow, and dosage must therefore be precisely adjusted.

It is apparent that the presently available preparations of ACTH in gelatin provide a highly effective means of producing intensive adrenocortical activation. Because of their convenience, it seems quite evident that these preparations should prove highly effective in the initiation of hormone therapy and particularly efficient in prolonged courses of maintenance treatment. In the latter connection, it is of interest that patients with chronic inflammatory diseases susceptible to the effects of steroid and ACTH treatment who are successfully maintained on comparatively large doses of cortisone or hydrocortisone may often be successfully maintained on comparatively small quantities (for example, 10 to 20 *U. S. P.* units) of ACTH in gelatin injected once daily and in some cases once every two days. In addition, the single daily injection of 40 to 80 *U. S. P.* units of the gel preparations for two days constitutes an excellent test for the integrity of adrenocortical function as measured by changes in circulating eosinophils and a rise in the urinary output of adrenocortical steroids.

(To be concluded)

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MEDICAL INTELLIGENCE

INTERNAL DRAINAGE OF PSEUDOCYST OF PANCREAS

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MERIDEN, CONNECTICUT

SINCE the first report of a successful anastomosis of a pseudocyst of the pancreas to the jejunum by Hahn[1] in 1927, this procedure has apparently become the treatment of choice for many surgeons. Only Meyer,[2] both of whose patients died of infection after operation, and Zieman[3] (1949) express discouragement.

The first successful applications of the Roux-Y principle to the operation of cystjejunostomy were reported almost simultaneously in 1948 by Gurwitz and Hurwitz,[4] Migliaccio and Laurelli[5] and Griesmann.[6] Since then, according to Moore and Schumacher,[7] there have been 9 additional cases in which the Roux-Y limb was successfully used, making a total of 12. Some have employed antecolic and others retrocolic anastomosis.

This report presents an additional successful case in an elderly patient with a thirty-three month follow-up period and good result. An unusual feature of this case was the fact that the anastomosis was performed anterior to the stomach rather than below it.

CASE REPORT

A 70-year-old woman was admitted to the hospital on August 7, 1949, because of upper abdominal distress of 24 hours' duration. She had suffered from recurrent attacks of this nature, with radiation through to the back, for 10 years. The attacks were precipitated by rich food and were accompanied by nausea and vomiting. A gastrointestinal series 4 years before admission had demonstrated a small pancreatic cyst. She had had mild diabetes for some time.

Physical examination showed an elderly woman who appeared acutely ill. The scleras were icteric. The abdomen was distended, with hyperactive peristalsis. There was tenderness in the region of the pancreas, where a rounded, hard mass about 15 cm. in diameter could be palpated.

The temperature was 99.6°F. by rectum, and the pulse 90. The blood pressure was 142/70.

Examination of the urine was negative. No bile was present, and the urobilinogen level was 0.32 mg. per 100 cc. The hemoglobin was 13 gm. per 100 cc., and the white-cell count was 12,000, with 88 per cent neutrophils. The blood sugar was 145 mg., the nonprotein nitrogen 28 mg., the serum albumin 4.23 gm., and the globulin 1.76 gm. per 100 cc. The icteric index was 19, and the serum amylase 273 mg., and the alkaline phosphatase 2.2 mg. per 100 cc.; the cephalin flocculation was +++. A stool did not show occult blood.

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The patient was treated with sedation for pain, restricted oral intake, intravenous infusion of fluids and antibiotics. She responded well to this management, but there was no decrease in the size of the mass. The icteric index fell to 6.4, and the amylase to 149 mg. per 100 cc., and the cephalin flocculation became negative. The white-cell count remained elevated (maximum of 15,000) with a high percentage of neutrophils (up to 91 per cent). A gastrointestinal series demonstrated a large mass consistent in location and appearance with a pancreatic cyst (Fig. 1).

Operation was performed on August 22. There was a large, firm, rounded, smooth mass in the region of the stomach, which was pushed downward and forward. It measured about 16 cm. in greatest diameter and was thick walled. The gall bladder showed some thickening in the serosa but was not distended, emptied well and apparently contained no stones. The liver had a normal appearance and was not enlarged. The gastrocolic omentum was opened in an attempt to expose a sufficient area of pancreatic cyst for anastomosis below and

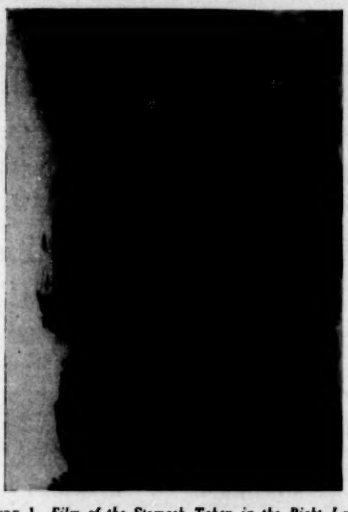

FIGURE 1. *Film of the Stomach Taken in the Right Lateral Position, Showing Anterior Displacement by the Pancreatic Cyst.*

behind the stomach. This was impossible because of the massive edema and dense adhesions present. The omentum was then closed, and the anastomosis made to the cyst anteriorly to the stomach. It was accomplished by transection of the jejunum about 15 cm. below the ligament of Treitz. The distal end was then anastomosed through the mesocolon and across the lower third of the stomach to the cyst, with 2 layers of nylon sutures. Before the anastomosis was completed, the cyst was opened, and its contents, which comprised about 1200 cc. of cloudy fluid, were evacuated. The continuity of the intestinal tract was then restored by anastomosis of the proximal section of the jejunum to the distal portion, end to side below the mesocolon.

Analysis of the fluid obtained from the cyst showed it to contain 656 mg. of reducing substance. A lipase determination yielded an amount sufficient to neutralize 1.07 cc. of twentieth-normal sodium hydroxide. A culture grew out *Escherichia coli*.

Gastric suction by Levine tube was continued for 60 hours after operation. The patient was out of bed on the 2d day. She was gradually put on a low-fat, high-protein, high-carbohydrate diet and given pancreatic substance after each meal. X-ray examination of the upper gastrointestinal tract before discharge revealed good function of the enterostomy and no barium entering the cyst (Fig. 2). Since the blood sugar did not go below 200 mg. per 100 cc., it was decided to maintain the patient on insulin.

After discharge from the hospital, she was carried on the same diet, supplemented by cod-liver oil, liver extract by mouth, thiamine and pancreatic substance. Painless jaundice was noted on September 30. The liver edge could not be palpated. Anorexia was present but no vomiting. The patient was kept on bed rest at home. On October 17, the 30-minute serum bilirubin was 34 mg., the icteric index 163 units, the alkaline phosphatase 6.1 units, the total protein 6.46 gm., the albumin 3.0 gm. and the globulin 3.46 gm. per 100 cc.; cephalin flocculation was ++++. On October

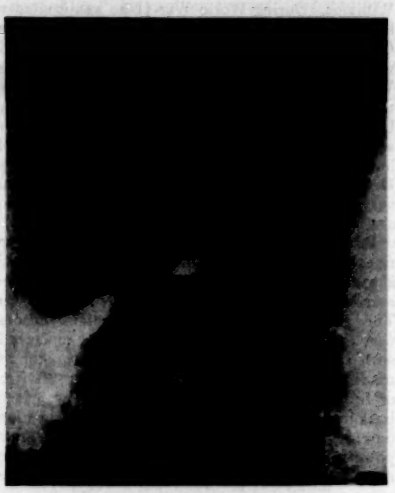

FIGURE 2. *Film Taken after Operation. There is no longer pressure on the stomach from the pancreatic cyst.*

19 the icteric index was 125 units, the total cholesterol 189 mg. per 100 cc., with 21 per cent esters, and the urinary urobilinogen 0.468 mg. per 100 cc.; the bile test being strongly positive.

The patient was given a protein supplement to her diet and continued on the same regimen. By January 4, 1950, the jaundice had cleared entirely, and she was feeling very well. On February 6 her weight was 110 pounds. At that time she was receiving 25 units of protamine insulin daily. By April 16 her weight had increased to 116 pounds, and on May 11 she weighed 121 pounds. The liver was now enlarged to palpation. The blood sugar was 340 mg., serum amylase 100 mg. (control 106 mg.), 30-minute serum bilirubin 0.5 mg., alkaline phosphatase 7.2 Bodansky units, total protein 6.47 gm., albumin 4.20 gm., globulin 2.27 gm., and total cholesterol 189 mg. per 100 cc., with 67 per cent esters, and the cephalin flocculation was ++. Protamine insulin was increased to 35 units daily.

On June 15, the liver edge had again receded, and the diabetes was well controlled on 35 units of protamine insulin a day. On January 30, 1951, the patient weighed 142 pounds, the blood sugar was 154 mg. per 100 cc., and examination of the urine was negative for sugar. On January 15, 1952, the patient complained of occasional slight back pain. The liver was not palpable. There was no epigastric mass or tenderness. Her weight was 140 pounds, and the blood sugar was 150 mg. per 100 cc. The diabetes was controlled with 25 units of NPH insulin daily.

DISCUSSION

A review of the reported cases of cystjejunostomy indicates a higher percentage of good results than for any other procedure employed in the treatment of pancreatic cyst except complete excision. In the 12 previous cases, as well as the case reported above, in which the Roux-Y principle was employed in anastomosis of the cyst to the jejunum, there was no operative mortality. Since complete excision is seldom practicable and is accompanied by a considerable mortality, it seems that in the management of moderate or large cysts, this operation should yield to cystjejunostomy utilizing the Roux-Y principle of anastomosis as the treatment of choice.

The poor results after marsupialization of pseudocysts and the high rate of recurrence are familiar to all abdominal surgeons. Excoriation of the skin, persistent drainage and pain may make the patient a chronic invalid and a social outcast. It is now possible to rehabilitate some of the unfortunate victims of this procedure by implantation of the fistulous tracts into the upper jejunum. The good results obtained by this procedure, which allows little or no regurgitation of bowel contents into the cyst because of the size of the tract, indicate that the prevention of back flow is important and provide further confirmation of the value of the Roux-Y principle, which permits the cyst to be anastomosed directly to the bowel.

SUMMARY AND CONCLUSION

A thirteenth successful case of cystjejunostomy, utilizing the Roux-Y principle of anastomosis in the treatment of a large pancreatic cyst, is reported. The anastomosis was made anterior to the stomach. The patient, who was seventy years old at the time of operation, had a good result almost three years after operation.

This method must now be considered the treatment of choice for moderate and large nonmalignant pancreatic cysts because of the uniformly good results obtained and the absence of operative mortality.

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DOCTORS AFIELD

William Carlos Williams

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RAY BROOK, NEW YORK

A BUSY pediatrician in Rutherford, New Jersey, William Carlos Williams has become during the past forty years one of the foremost American writers. He is noted for his fresh, unconventional poems, plays, novels and short stories.

Williams became interested in writing and the arts at about the same time that he chose medicine as a profession. He decided that his artistic interest need not prevent his studying to be a doctor, and he went ahead with both. His first poem was written over fifty years ago, "born like a bolt out of the blue," he says. "From that moment I was a poet."[1]

He graduated from the University of Pennsylvania School of Medicine in 1906, interning at the old French Hospital in New York City and then

at the Nursery and Child's Hospital. During his training he continued to write, his first book, *Poems*, being published in 1909. He then went to Leipzig for a year of postgraduate study.

Returning to this country, Williams settled down to practice and write in Rutherford. He married and bought the house where he has lived ever since. On two more European trips he formed and maintained friendships among literary and artistic figures, including Robert McAlmon, Ezra Pound, James Joyce, Gertrude Stein and Ernest Hemingway. By communicating with poets and artists through the years, he has remained constantly in touch with contemporary art.

Much of his early work was published in the "little" literary magazines, to which he acknowledges a great debt.[2] He followed six collections of poems with a novel, and then wrote *In the American Grain* (1925). This comprised a series of episodes in American history with "ingenious imbedding of authentic source materials."[3] More novels and poems came out, joined now by plays. Eventually, over thirty of his books were published, including a trilogy of novels, and his poems are widely anthologized.

Williams only gradually became recognized by "a devoted if small following among the most brilliant young literary men in the country."[4] He received an award from *Poetry* magazine in 1924 and from *The Dial* in 1926. As time went on, the literary world awoke to pay tribute to Dr. Williams. During World War II he was invited to lecture at colleges and universities on the East Coast. The list grew, and he traveled with his wife to Puerto Rico and, in 1950, to schools in the West. He received honorary degrees from Rutgers, the University of Buffalo, Bard College and the University of Pennsylvania. In January, 1953, he and Archibald MacLeish were awarded the Bollingen Poetry Prize by the Yale University Library. Dr. Williams will be seventy this year, and until very recently his health permitted him to practice and write actively.

Practically all his writing stands out as perceptive, arresting and honest. He is concerned with subjects as varied as childbirth, death, moral and social issues, and the exquisite beauty of a flower. The poem "Tract" cuts away the false decoration attending a funeral procession and replaces it with simpler and deeper emotion. The doctor attending an immigrant family in the story "A Face of Stone" comes gradually to realize how grim a background they had and how it led to their apparently insolent manners. His prose is direct, powerful, unadorned and witty in its understatement. Yet "it is in poetry that Williams' achievement promises to be most enduring."[5]

Williams has made many contributions to poetry. He recognizes the importance of the visual structure of a poem, as well as the placing of his words and punctuation on the page to achieve a striking result. A poet, he believes, works with both the meaning and the sound of words, building his line of syllables so that it becomes a unit of sound-meaning relations.[6] "The line comes from the breath," he says, "from the breathing of the man who writes."[7]

Perhaps most important is his insistence on the "new" and the "local" events as subject material for the poet. This brings critics to exclaim at his originality.

Williams made the following remarks to a group of Dartmouth students[8]:

> . . .I believe all art begins in the local and must begin there since only then will the senses find their material. Our own language is the beginning of that which makes and will continue to make an American poetry distinctive—

As a consequence in some of my work all I have to do is to transcribe the language when hot and feelingly spoken. For when it is charged with emotion it has a tendency to be rhythmic, lowdown, inherent in the place where it is being used.

He is a consciously American writer, his awareness being partly attributable to the European experiences.[9]

It has puzzled many people that Williams was able to carry on two tremendous jobs, either of them more than adequate to keep most men permanently out of mischief. "When they ask me, as of late they so frequently do, how I have for so many years continued an equal interest in medicine and the poem, I reply that they amount for me to nearly the same thing." He explains further: "I found by practice, by trial and error, that to treat a man as something to which surgery, drugs and hoodoo applied was an indifferent matter; to treat him as material for a work of art made him somehow come alive for me."[10] He found also that intense application to his practice actually rested him. For much of his writing he kept a typewriter in his office: I worked at top speed. If a patient came in at the door while I was in the middle of a sentence, bang would go the machine — I was a doctor. . . .Finally, after eleven at night, when the last patient had been put to bed, I could always find time to bang out ten or twelve pages.[11]

How does it feel to look back on forty years of practice and writing? Williams himself simply says that there is a great deal more to be written. Poetry and medicine have greatly benefited from his devoted service, and both may take pride in his achievements at this end of a long and colorful career.

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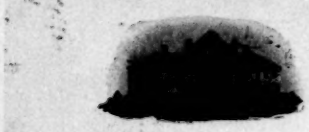
CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39141

Presentation of Case

A seventy-year-old Negro laborer was admitted to the hospital because of jaundice and hepatomegaly.

The patient was in good health until three and a half weeks before admission, when he began to have intermittent right-upper-quadrant pains unrelated to meals. At about the same time he noticed that his urine became dark. There was no dysuria. Two weeks before admission, when a fever developed, he consulted his physician, who found icterus, hepatomegaly, fever and "high blood pressure." The temperature dropped after treatment with penicillin. The patient noticed that his stools became gray. There had been no history of food intolerances, change in bowel habit or melena. At the time he consulted his physician, the patient, on two occasions, vomited clear fluid, but he had not done so before or since. There was no hematemesis. He had had a good dietary intake, but had taken a pint of wine a day for years. He had no chills, backache, fatigue, weakness, pedal edema, epistaxis or recent injections. He denied bruising easily. For the past two weeks he had noticed that his abdomen was protuberant.

Physical examination revealed a heavily jaundiced, dehydrated man in no acute distress. The scleras were icteric; the eyes were prominent and showed lid lag. The fundi demonstrated tortuous constricted arterioles, with some exudates. The throat was injected and coated with exudate; the teeth were carious. Chest expansion was limited by high leaves of the diaphragm; there were dullness and decreased tactile fremitus at both bases, with diminished breath sounds and medium moist crackling rales. The heart was enlarged, with the point of maximum impulse 11.5 cm. to the left of the midsternal line. The aortic second sound was greater than the pulmonic; no murmurs were heard. The abdomen was tense, with shifting dullness. The liver edge was palpable 5 cm. below the right costal margin in the midclavicular line. It was smooth and slightly tender. The spleen was not palpable; there were no masses, venous distention or vascular spiders. The remainder of the examination was negative.

The temperature was 99.6°F., the pulse 120, and the respirations 26. The blood pressure was 160 systolic, 80 diastolic.

The urine was brown, had a specific gravity of 1.020 and gave a ++++ test for bile and negative tests for albumin and sugar; the sediment contained 2 to 5 white cells and granular casts per high-power field. Examination of the blood showed a hemoglobin of 10 gm. per 100 cc. and a white-cell count of 15,000, with 90 per cent neutrophils, 8 per cent lymphocytes and 2 per cent monocytes. The sedimentation rate was 65 mm. per hour, and the hematocrit 24 per cent. The serum sodium was 130 milliequiv., the potassium 4.9 milliequiv., the carbon dioxide 25 milliequiv., and the chloride 98 milliequiv. per liter;

FIGURE 1.

the nonprotein nitrogen was 34 mg., the total protein 5.6 gm., the albumin 2.6 gm., the globulin 3.0 gm., the serum bilirubin 11.2 mg. direct and 14.1 mg. total, and the alkaline phosphatase 16.9 units per 100 cc. The prothrombin time was 26 seconds (24 per cent of normal). The cephalin flocculation was ++ in twenty-four and forty-eight hours. A culture of the urine showed no growth. A stool specimen was gray and guaiac negative. A blood Hinton test was negative. An electrocardiogram disclosed a rate of 120 per minute, a PR interval of 0.08 to 0.10 second, a QRS interval of 0.12 second, one auricular premature beat, normal voltage, left-axis deviation and notching of the P waves and low T waves in Leads AVL and V_5. Roentgenograms of the chest revealed prominence of the heart in the region of the left ventricle. The right side of the diaphragm was considerably elevated, and there was a suggestion of atelectasis of the right lower lobe (Fig. 1 and 2). On a plain film of the abdomen the liver margin was not clearly seen. There were gas-distended loops of small bowel in the middle and left sides of the abdomen. A small amount of gas also appeared to be present in the cecum, probably in the splenic flexure. The right-psoas-muscle shadow was not clearly seen.

By the third hospital day, the patient complained of more abdominal pain, and began to vomit. The abdomen was more distended and on examination was tender and tympanitic, with moderate spasm everywhere. Peristalsis was absent. The temperature was 101°F., the pulse 110, and the respirations 40. The nonprotein nitrogen had risen to 75 mg. per 100 cc.

On the following day his condition was about the same. Fluid intake was 4500 cc., with an output of 1000 cc. The nonprotein nitrogen was 90 mg. per 100 cc. Twenty-four hours later the white-cell count was 29,500, and despite the passage of a Miller–Abbott tube the abdomen was still somewhat distended. Sigmoidoscopic examination was negative. Therapy consisted of transfusions, intravenous fluids, Hykinone, penicillin and streptomycin.

FIGURE 2.

On the seventh hospital day the patient had crampy abdominal pain; there were few bowel sounds, but the abdomen, which had been tense, felt softer. The abdomen continued to be distended, quiet and tender. The tenderness was most marked in the lower quadrants. The leukocyte count rose to 32,000, and the temperature remained at about 100°F. On the ninth hospital day, after having vomited brown gastric contents, the patient died.

DIFFERENTIAL DIAGNOSIS

DR. CLAUDE E. WELCH*: I might say first that I am confused about the diagnosis. There certainly

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appear to be enough data in the history for me to make a diagnosis; yet, when one tries to select a diagnosis, there are just enough atypical features for each condition to make the final choice somewhat difficult.

I shall review the history to pick out the salient features and see how they fit best. From the outset, we might suspect that the history would be somewhat meager and perhaps somewhat inaccurate; these elderly men are prone to forget what happened in the past. His age is of interest because we think of the possibility of cancer rather than diseases that commonly involve the liver in youth. The jaundice and hepatomegaly point directly to the liver. If I can believe the history, he was in good health until three and a half weeks before admission. This short history is not what one would expect with long-standing cirrhosis, for example. Then he began to have intermittent right-upper-quadrant pain, which is suggestive of some obstruction to the common duct, such as a stone. But, as all of us know, right-upper-quadrant pain may be present in any type of liver disease and may be of practically the same character whether it is caused by stone, cirrhosis or metastatic cancer. The symptoms of obstruction of the common duct then appeared, with dark urine and later gray stools. After he had the pain and after he had the jaundice, the fever developed. There was some vomiting and many negative findings, which are of interest in ruling out previous liver disease. Then, when the patient came into the hospital, the most important factors were the high diaphragm, the large liver and the shifting dullness, about which apparently there was no question; in other words, he apparently entered the hospital with ascites of undetermined cause. Nevertheless, there was no palpable spleen and no other confirmatory evidence of cirrhosis.

The important data in the laboratory studies indicate that he did not have much fever on admission; the temperature was 99.6°F. The moderate anemia — the hemoglobin was only 10 gm. per 100 cc. — is somewhat surprising in view of the short history. The white-cell count was definitely elevated, and the 90 per cent neutrophils is of a good deal of interest in the differential diagnosis. The sedimentation rate was exceptionally high. The important blood chemical findings in the differential diagnosis are the low total protein, the reversed albumin-globulin ratio and the high serum bilirubin and alkaline phosphatase. The prothrombin time was also grossly abnormal, but I do not know whether or not it remained abnormal after the administration of vitamin K. The flocculation test was what we call normal, being ++ in twenty-four and forty-eight hours. The electrocardiogram was not remarkable.

May I see the x-ray films?

DR. STANLEY M. WYMAN: The films of the chest were made with the patient lying on his back so the heart size is somewhat magnified; nevertheless, there is enlargement of the left ventricle and some tortuosity of the aorta. The fairly striking prominence of the right leaf of the diaphragm, which is elevated and domed anteriorly, is quite well seen (Fig. 1 and 2).

DR. WELCH: There probably was no fluoroscopy of the chest.

DR. WYMAN: No; therefore I cannot tell you anything about the motion of the diaphragm.

DR. WELCH: Was there any fluid in the chest?

DR. WYMAN: There is minimal atelectasis from compression by the high diaphragm. The costophrenic angle is clear, and as far as I can see, there is no fluid. The films of the abdomen made on successive days up to the time of death show persistent dilatation of many loops of small bowel and perhaps a slight amount of gas in the ascending colon. The liver, I think, is enlarged, coming down to about this point. There are no abnormal masses that I can detect in the abdomen. The folds of the small bowel are somewhat separated on some of the later examinations, which is, perhaps, in keeping with the increase of fluid in the peritoneal space.

DR. WELCH: It is not as striking as one might expect in the presence of a great deal of ascites?

DR. WYMAN: I suspect these loops are floating upon the fluid.

DR. WELCH: At this point in the protocol it might be wise to take stock. I think that probably at that moment the patient had been admitted for study and was receiving a more or less leisurely work-up. Everything seemed to be going fairly well, and probably a liver biopsy was planned in the course of the next few days to determine whether he really had hepatitis. Then, suddenly, there seemed to be a dramatic change, which stopped all further diagnostic procedures. Apparently, he was too sick for operation even to be considered, and he died.

The problem is to determine whether the manifestations of disease were due to one disease or whether on the third hospital day something else happened and there was a superimposed disease. At any rate, on that day, abdominal pain became more marked, and the abdomen became more distended, with spasm and absence of peristalsis — that is, definite signs of peritonitis and intestinal obstruction appeared. It is clear that the patient rapidly became much sicker. I think, in retrospect, it is fair to suggest that one might wish that an exploratory laparotomy had been performed on the third hospital day from the point of view of establishing a diagnosis. Be that as it may, the only information is that the patient finally died of peritonitis and obstruction.

What was the underlying disease that was causing all this difficulty? I think I had better pick out only three or four possibilities to discuss. In the first place I shall divide the possibilities into three: lesions primary in the liver, primary in the common

duct and primarily extrahepatic, with the involvement of the liver in a secondary fashion. If this man's disease was primary in the liver, it would be very unlikely for him to have had an ordinary cirrhosis or cirrhosis complicated by hepatoma with metastases. I suspect that the admitting diagnosis and the treatment for the first three days was predicated on the possibility that he had an acute hepatitis of the epidemic type. Every effort to make a diagnosis of homologous serum jaundice apparently was made, and it could not be done. There are several features that are somewhat atypical for this particular diagnosis. Of course, patients with severe hepatitis may have pain of this nature and may have completely obstructed ducts, with gray stools, but that is somewhat unusual. A hemoglobin of 10 gm. is also unusual with acute hepatitis of three weeks' duration. The differential count is somewhat against that diagnosis. If this man had an acute hepatitis there is no way I can account for the progress after the third hospital day except to assume that he had a separate lesion starting on that day, and I should prefer to make a single diagnosis.

The second possibility is that the lesion was primary somewhere in the extrahepatic biliary system. Among the two or three possibilities that one might like to consider is a gallstone that had produced blocking of the common duct and that was large enough to ulcerate finally into the small bowel, where it caused acute obstruction. That is a speculative chance. A common-duct stone per se, resulting in biliary cirrhosis and ascites and finally death from peritonitis, might be possible; again, this is certainly not a usual picture. Nor is the picture typical of carcinoma of the head of the pancreas, which I ought to consider fairly strongly in this particular case. Obstructive jaundice from carcinoma of the head of the pancreas could have developed, with metastases to the liver and ascites, and the patient could have died with terminal peritonitis. Yet the final course was not the usual one of a patient with carcinoma of the head of the pancreas that had metastasized to the liver.

The third possibility is extrahepatic disease, under which some type of inflammatory lesion and tumor must be considered. If this was an inflammatory lesion, the only guide to its origin was furnished by the short, late course of the patient, with symptoms more localized to the lower than to the upper abdomen. One diagnosis that should always be kept in mind in such a patient, is appendicitis, with pylephlebitis and finally death from peritonitis and liver abscesses. There are, however, a number of objections to that particular diagnosis. Usually, when such a patient enters the hospital, the temperature is much higher than this patient's was. If I can believe that the sequence of symptoms was as the patient described them — that is, right-upper-quadrant pain, followed first by jaundice and then by fever — they were not typical of a pylephlebitis, with which fever is practically always the original symptom. Even so, this is one diagnosis that I have to consider fairly seriously because this patient, who was old, may have been hazy about his history.

Could the cancer have originated in some other site in the abdomen, with metastasis to the liver? That would account for a great number of the features. For example, it would account for the fact that the patient seemed to be more chronically ill than he should have been with a three-week history and for the hemoglobin of 10 gm., as well as for the large liver and the abnormal findings in the laboratory studies, particularly the high sedimentation rate, which goes with advanced cancer. One unusual feature, it must be admitted, was the complete obstructive jaundice, which is not too common with metastatic disease. Such jaundice is usually produced by definite obstruction in the head of the pancreas. Carcinoma, if it originated from the colon, could have caused some of the symptoms, — for example, the ascites that the patient had when he entered the hospital, — and if the primary lesion was in the cecum, it could have resulted in a final slow perforation and peritonitis, with advancing intestinal obstruction and death.

Having pointed out that every diagnosis has some disadvantages, I think I shall choose as my preference carcinoma originating in the colon, metastatic to the liver, and shall say that the patient died of intestinal obstruction and peritonitis.

DR. LELAND S. MCKITTRICK: I saw this patient with the students a few days before he died; I must confess that it was not a wise selection to present to the students if one wanted to demonstrate any particular diagnostic acumen because it was totally impossible for me to make a logical diagnosis. He was acutely ill; his history was short; and I thought he would die within a day or two, which he did. This patient, who had been well until recently, was now dying. He was completely jaundiced, was distended, had free fluid and had dilated bowel, which I thought was probably ileus rather than obstruction. Whether it was ileus or whether it was obstruction did not seem to make much difference in the treatment so it was not worth while to try to find out. I tried to explain the picture on the basis of liver disease but I could not determine why the liver seemed to be so large. When one stood away from the patient, one could see a large mass that had the shape of an enormous liver. We did not know the response of the prothrombin time to vitamin K at that time. I could not understand how the patient could be dying of acute liver disease and have what looked like such a large liver. It seemed to me that there was some other problem, either a complication of the original disease or a second disease. The possibility of an abscess was considered but not too seriously. Nothing further was done to make a diagnosis, and we ended up without an accurate diagnosis but I believed it was

not an uncomplicated common-duct stone or cancer of the biliary tree or of the pancreas. I did not see how it could have been wholly explained on the basis of intrahepatic disease.

A PHYSICIAN: Does Dr. Welch have any explanation for the nonprotein nitrogen level?

DR. WELCH: I assumed that it was rising on the basis of the peritonitis. The urine was not too bad; the specific gravity was 1.020, and the sediment contained only a few granular casts, so there was no reason to believe that the patient had any intrinsic renal disease.

DR. DANIEL S. ELLIS: I had made one diagnosis but after listening to Dr. McKittrick's description of the size of the liver, I am going to say that I favor metastatic disease of the liver.

DR. MCKITTRICK: Let me correct that; it was a mass that I interpreted to be a large liver. This mass went across the epigastrium and down over the right flank, just as it does in the plain film, and looked to me as though it followed the contour of the liver.

DR. ELLIS: It did not feel like distended bowel?

DR. MCKITTRICK: No; I thought that it was liver, and I am not saying that it was not. Is it possible for a person dying with intrahepatic disease — so-called yellow atrophy or whatever it is called now — to have a large liver?

DR. ELLIS: Yes; a patient could have a large liver and be dying from liver disease, but I do not think this patient was dying from that kind of liver disease.

DR. MCKITTRICK: It was not recorded in the protocol or in the record when I saw him, but the prothrombin time promptly responded to vitamin K. I should assume that this almost excluded serious hepatocellular disease.

DR. JOHN T. STANBURY: This process was known to have been present for only two and a half weeks. How soon is there reversal of the albumin-globulin ratio? Does that suggest that he had long-standing liver disease?

DR. ELLIS: Not necessarily. The other conditions that could cause it are carcinoma of long standing and chronic sepsis.

CLINICAL DIAGNOSES

Obstructive jaundice.
Intestinal obstruction.
?Carcinoma.
?Gallstone ileus.

DR. CLAUDE E. WELCH'S DIAGNOSES

Carcinoma of colon, with metastases to liver.
Intestinal obstruction.
Peritonitis.

ANATOMICAL DIAGNOSES

Adenocarcinoma of common bile duct.
Hydrohepatosis with multiple liver abscesses.
Peritonitis, with subdiaphragmatic and infradiaphragmatic abscesses.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: When the abdomen was opened, the prosector immediately noted infection. There was about 3000 cc. of fluid in the abdomen, about half of which was located under the right leaf of the diaphragm as a large subdiaphragmatic abscess. That abscess was not as purulent as another abscess in the infrahepatic area that contained about 1000 cc. of fluid. I believe that this large abscess rather than the liver was being felt. There was also about 500 to 1000 cc. of fluid in the general abdominal cavity.

DR. MCKITTRICK: Was that pus?

DR. CASTLEMAN: It was not too purulent, but certainly it was infected. When that was cleared away, we looked at the gall-bladder bed, believing we should find a perforated gall bladder. The gall bladder was distended and covered with exudate, but the wall and the mucosa were normal. Further dissection showed obstruction to the common duct by a small, stenosing carcinoma at the lower end of the common bile duct. The dilatation of the common bile duct extended into the liver so that there was a severe hydrohepatosis, all the radicles within the liver being dilated and infected. Sections through the liver showed a number of abscesses, more numerous on the left side than on the right. Many of them were close to the surface of the liver, and one or two of them probably led to the production of the abscesses within the abdomen.

I had not been impressed with the fact that common-duct obstruction often led to sepsis within the liver but a review of the cases from the Boston City Hospital[1] and many from other Boston hospitals[2] showed that it does occur. Kinney and Ferrebee[2] noted that 50 of 263 cases of liver abscess followed common-duct obstruction, and a number of these cases were complicated by peritonitis.

DR. MCKITTRICK: Was there a point of intestinal obstruction? That is a striking x-ray picture.

DR. CASTLEMAN: No; it was all ileus. The microscopical sections of the gall bladder gave no evidence of infection. The wall and the mucosa looked normal, so I do not believe that we missed a perforation that had sealed over.

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CASE 39142

PRESENTATION OF CASE

A twenty-four-year-old truck driver entered the hospital because of back pain, weakness, nausea, vomiting and weight loss.

The patient had been well until four months before entry, when he began to have constant back pain that radiated across the back but not anywhere else. Two days later, he had a sudden onset of severe pain, redness, swelling and tenderness of the left testis lasting for three days. Again, two days later, he had an excruciating pain in the right elbow. The pain was aggravated by motion and lasted for three days, when it moved to the knees, shoulders and back of the neck, each episode lasting for three or four days. Local application of heat helped the pain temporarily. It stopped after he had taken certain "big green pills" given by his physician, but recurred with less severity five weeks before admission. About three months before entry he began to notice slight exertional dyspnea, weakness and occasional ankle edema. Meanwhile, the urine was observed to be dark orange, and he began to have polyuria and nocturia. A burning sensation on urination was experienced only once, but there was dribbling of urine after each urination. About seven weeks before entry he began to have severe epigastric pain, associated with nausea and vomiting, one to four times a day. A gastrointestinal series was done in another hospital, but showed nothing abnormal. Five weeks before admission the right leg became weak and numb, and he limped; there was paresthesia of the fingers and toes. A week later, he began to have throbbing bilateral parietal headache, radiating to the temporal region and the back of the neck. A week before entry, he was examined by another physician, who told him that he had a high blood pressure. He had lost about 30 pounds of weight, and his symptoms persisted up to the time of entry.

The patient had been accustomed to drink 15 to 20 glasses of beer a day since seventeen years of age, but he had always been well, except for some urethral discharge about four years before admission, for which he received three penicillin injections. When he was discharged from the Army four years before admission, he was told that his physical condition was perfect and that his blood pressure and urine were both normal.

On physical examination the patient appeared acutely and chronically ill, but was alert and well oriented. There were generalized palpable, small, discrete superficial lymph nodes. A small hemorrhagic spot was seen in the left optic fundus. The lungs were clear. The heart had a soft systolic blowing over the entire precordium and a faint gallop at the left sternal border in the fourth intercostal space. There was marked tenderness and spasm in the epigastrium, but no mass or organ was felt. The left gastrocnemius muscle was tender, and there was diminution of pain sensation on the outer surface of the upper arms and right upper thigh and below the left knee. Both testes were small, and the left one was flabby.

The temperature was 102°F., the pulse 110, and the respirations 28. The blood pressure was 170 systolic, 120 diastolic.

The urine had a specific gravity of 1.015 and gave a ++++ test for albumin; the sediment contained a few casts, red cells and white cells per high-power field. The urine had a fixed specific gravity of 1.006. Examination of the blood showed a hemoglobin of 12.5 gm. and a white-cell count of 15,000, with 85 per cent neutrophils, 9 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils. The cephalin flocculation was ++ in twenty-four and forty-eight hours. The nonprotein nitrogen was 25 mg., the total protein 6.52 gm., with an albumin-globulin ratio of 1.3, the calcium 9.2 mg., the phosphorus 3.5 mg., the alkaline phosphatase 7.1 units, and the fasting blood sugar 150 mg. per

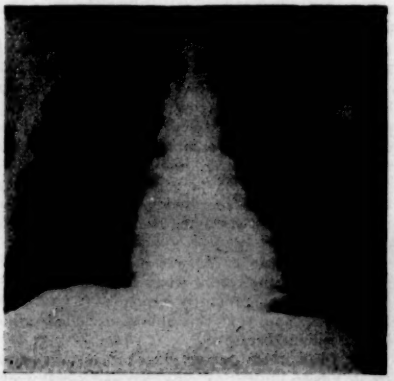

FIGURE 1.

100 cc. (One week later the fasting blood sugar was 87 mg. per 100 cc.) The sedimentation rate was 1.9 mm. per minute. An eosinophil count was 234 per cubic millimeter. Lupus-erythematosus cells were not found in a peripheral blood smear. Phenolsulfonephthalein excretion was 18 per cent in two hours. The vomitus was brown and watery, giving a ++ guaiac test. A stool guaiac test was negative. Examination of the sputum revealed many gram-positive cocci, but acid-fast organisms were not found. Urine and blood culture showed no growth. Agglutination tests for febrile antigens were negative. Biopsy of the left gastrocnemius muscle, skin and right axillary lymph nodes showed no diagnostic abnormalities. Chest roentgenograms (Fig. 1), gastrointestinal series and an intravenous pyelogram were normal. X-ray examination of the skull revealed areas of rarefaction in the

left occiput of doubtful significance, and thickening of the mucous membrane of the antral sinuses with a fluid level in the left. An electrocardiogram demonstrated many premature ventricular contractions.

The patient continued to have epigastric distress, and vomited and coughed frequently. Sedation and tincture of belladonna gave slight relief from the abdominal discomfort, and aspirin eased the backache. On the eleventh day, he was found to have ++ edema of the feet, and on the thirteenth day, he had a sudden onset of dyspnea associated with high-pitched wheezing in both inspiratory and expiratory periods. A few coarse rales were audible

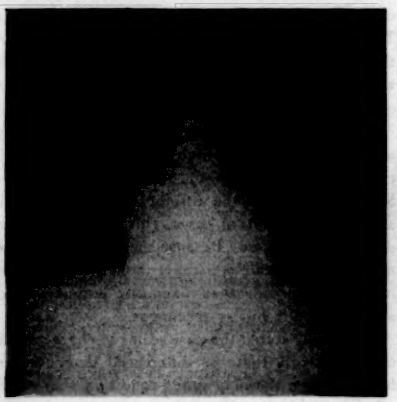

FIGURE 2.

in the lung bases. X-ray films of the chest on the same day showed "bat-wing" shadows of the lung and a small amount of fluid in the right pleural cavity (Fig 2). On the next day, he began to cough up blood-tinged sputum, and had +++ ankle edema. However the venous pressure was normal (85 mm.). ACTH (adrenocorticotrophic hormone), 25 mg. intravenously, was started on the fifteenth day. The episodes of dyspnea recurred frequently and were only slightly relieved by epinephrine and aminophylline injections. Rhonchi and wheezing were audible, but there were very few moist rales. He was digitalized and later placed in an oxygen tent. An electrocardiogram then revealed nonspecific low T waves in Leads 1, 2, V_5, V_6 and AVL and flat T waves in Leads 3 and AVF. The cardiac rhythm was normal. On the same day the blood sodium was 120.6 milliequiv., the chloride 78 milliequiv., the potassium 4.4 milliequiv., and the carbon dioxide 28.3 milliequiv. per liter; the nonprotein nitrogen was 68 mg. per 100 cc., and the blood pH was 7.58. He was given salt orally. On the nineteenth day, therapy was changed from ACTH to cortisone, and a small amount of saline solution was given intravenously. In spite of these measures the patient continued to have dyspnea, vomiting and increasing edema and pursued a steadily downhill course. On the twenty-seventh day the serum sodium was 113.5 milliequiv., the chloride 82 milliequiv., the potassium 6.5 milliequiv., and the carbon dioxide 21.6 milliequiv. per liter, and the nonprotein nitrogen 190 mg. per 100 cc. On the following day he died.

DIFFERENTIAL DIAGNOSIS

DR. ALEXANDER LEAF*: This case gives clear evidence of involvement of multiple systems and organs during the four months' duration of the fatal illness. The protocol indicates involvement of joints, testis, heart, kidneys, gastrointestinal tract, peripheral nerves and lungs. In addition the patient had fever, leukocytosis, weakness, malaise, marked weight loss and hypertension. The extensive involvement of many systems here makes it seem most likely to me that the patient had diffuse vascular disease.

May I see the x-ray films?

DR. LAWRENCE L. ROBBINS: The pertinent films are the chest examinations; between the first (Fig. 1) and thirteenth (Fig. 2) hospital days, there is a marked change in the appearance of the lung fields and the heart. The heart has increased in size somewhat, and in the central portions of the lung fields there is diffuse haziness. This appearance is frequently seen in acute pulmonary edema from a variety of causes. The short interval in which the changes appeared suggests that this is an acute process.

DR. LEAF: Almost all the symptoms and findings, as well as the course of this patient's ailment, are characteristic of polyarteritis nodosa. This patient was a man, and about 80 per cent of patient's with this disease are males. The migratory joint pains early in the course of the illness may

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have represented part of the diffuse vascular involvement of polyarteritis, or they may have been due to the presence of associated acute rheumatic fever. The not too infrequent coincidence of these two conditions has been reported.[1]

Abdominal symptoms such as this patient exhibited are common in polyarteritis and are due to involvement of intestinal and mesenteric vessels. The guaiac-positive vomitus indicates rupture of an aneurysm or of a weakened arterial wall in the upper gastrointestinal tract.

The neuritis suggested by weakness and numbness of the right leg with paresthesias of the fingers and toes and diminution of pain sensation on the outer surface of the upper arms and right upper thigh and below the left knee is characteristic of the patchy distribution of the peripheral neuritis seen in polyarteritis. Unfortunately, no mention of reflexes or muscle strength in the involved right leg was made in the examination.

Renal disease characterized in this case by polyuria, nocturia fixed specific gravity and albuminuria, with casts and red cells in the sediment, reduced phenolsulphonephthalein excretion and terminal uremia, is perhaps the most constant finding in polyarteritis. Renal involvement is present in about 80 per cent of cases. Davson, Ball and Platt[2] have subdivided the renal involvement into two groups. In the first, vascular lesions characteristic of the acute phase of polyarteritis are found in the kidneys or other organs, or both, and the renal parenchymal lesions are those of widespread necrotizing glomerular lesions. The course of the renal lesion is one of progressive uremia, without development of hypertension. In the second group there is vascular necrosis with perivascular infiltrations involving medium-sized vessels as well as arterioles and no extensive involvement of glomeruli. This second group has a higher incidence of hypertension, which in some cases is thought to be attributable to the obstructive healed lesions of polyarteritis nodosa in the larger renal vessels causing ischemia and hence hypertension analogous to that produced by Goldblatt in animals. The patient under discussion had severe hypertension, with glomerular failure occurring late, as evidenced by the elevated nonprotein nitrogen terminally. Hence, clinically at least, this case falls in the second group of Davson et al. The not uncommon finding of the association of the lesions of glomerulonephritis together with those of polyarteritis nodosa in the experimental production of the latter in the rabbit by Rich and Gregory[3] suggests that etiologically these two conditions may be closely related.

This patient had pulmonary symptoms that may have been due to involvement of pulmonary vessels by polyarteritis or to congestive heart failure. The high-pitched inspiratory and expiratory wheezes with dyspnea, occurring at a time when the venous pressure was allegedly still normal, suggest bronchial asthma, which is common in polyarteritis nodosa. The use of epinephrine to treat the asthma indicates that the attending physicians likewise thought that the asthma was due to bronchial spasm and not to congestive heart failure. The blood-tinged sputum is possibly attributable to pulmonary infarcts from involvement of the pulmonary vessels by the pathologic process or to pulmonary congestion alone. Terminally, however, it seems from the protocol that the patient did have congestive heart failure, with increasing edema and decreasing concentration of serum sodium.

The only findings against a diagnosis of polyarteritis nodosa are the absence of an increase in circulating eosinophils and the negative biopsies. Since elevation of the eosinophils occurs only in about 20 per cent of cases, this negative finding does not disturb me. Because the vascular involvement in this disease is patchy, though often diffuse, it is not surprising that diagnostic lesions are not always found in biopsy specimens.

As initially stated this case seems so characteristic of polyarteritis that the differential diagnoses are few. Perhaps the only other condition that might mimic the findings is subacute bacterial endocarditis. The sterile blood cultures are against this diagnosis.

Dr. Greene Fitzhugh: This patient was thought to have chronic nephritis, polyarteritis, however, being considered a distinct possibility. Later on in his hospital course as the clinical picture unfolded, polyarteritis was considered to be the most probable diagnosis, with nephritis as a possibility. It was not believed that the absence of polyarteritis in the biopsy specimen should rule out polyarteritis. From the point of view of therapy, we were cautious in administering hypertonic saline solution because of the progressing congestive heart failure. This was considered wise in spite of the steadily falling blood sodium and chloride.

DR. FARAHE MALOOF: Because of the patient's abnormal mental state, which was a dominant feature of his illness, it was difficult to evaluate many of his symptoms. There were several findings that were not explained by renal disease alone, and hence soon after admission most of us favored polyarteritis nodosa. Dr. William Cobbs, Jr., a medical intern, made this diagnosis when he first saw the patient in the Emergency Ward.

The pulmonary findings were interesting. Initially, the signs were those of bronchial asthma, and the symptoms responded to epinephrine. Soon after peripheral edema, pulmonary congestion and cardiac asthma, which required appropriate cardiac therapy, developed.

CLINICAL DIAGNOSIS

Polyarteritis nodosa.

DR. ALEXANDER LEAF'S DIAGNOSIS

Polyarteritis nodosa, with involvement of kidneys, gastrointestinal tract, peripheral nerves, testis, and possibly heart, liver and lungs.

ANATOMICAL DIAGNOSES

Polyarteritis nodosa, healing and healed, generalized.
Renal infarcts.
Granulomatous pneumonitis, with organization, ?polyarteritis nodosa.
Cardiac hypertrophy, left and right ventricles.
Epicarditis, healed.
Generalized lymphadenopathy.

PATHOLOGICAL DISCUSSION

DR. DAVID KAHN: Autopsy revealed classic polyarteritis nodosa in which the lesions presented as gross nodules involving muscular arteries of the magnitude of the hepatic artery and less. Multiple nodules measuring up to 0.6 cm. in average diameter were scattered along the course of the following arteries: primary branches of the coronary arteries, hepatic artery and its branches, mesenteric arteries, intrarenal branches of the renal arteries, and spermatic arteries. On sectioning, the nodules were eccentrically placed thickenings of the arterial walls, and at the level of these, the arterial lumens were either severely narrowed or completely occluded by a dark-red thrombus. In only two locations was there gross evidence of parenchymatous damage as a result of this vascular involvement; throughout both kidneys there were multiple 1-cm. discrete cortical infarcts, and the testicles were small and showed small areas of infarction. Other gross findings of interest were generalized lymphadenopathy, cardiac hypertrophy (the heart weighed 420 gm.) with hypertrophy of both left and right ventricles, and severe pulmonary edema and congestion (the weight of the lungs was 2200 gm.)

Microscopical examination showed the vascular lesions to be segmental, with involvement of arteries with diameters between 0.3 cm. and 300 microns. In addition to those seen on gross examination lesions were found in arteries in the periadrenal tissue, pancreas and striated muscle, and in the nutrient arteries of peripheral nerves. The lesions were either in a healing stage or completely healed; no acute or subacute stages were found. In the healing lesions aneurysmal dilatation on the side of the destroyed media was seen. The lumens contained organized thrombi, which were in direct continuity through a fragmented internal elastic membrane with granulation tissue replacing the destroyed media and involving the adventitia. The process varied from early repair with young granulation tissue through to the completely healed lesions, which showed segments of destroyed media completely replaced by dense fibrous tissue that was continuous out into the adventitia and inward into the lumen, so that the latter was completely occluded and contained a number of eccentrically placed, recanalized small lumens. A third type of arterial change was that of a markedly thickened cellular intima with a narrowed central lumen; the remainder of the arterial wall was normal and had an intact internal elastic membrane. This has been described[3] as the change found in arteries just proximal and distal to an involved arterial segment; in this case this change was widespread, was most common and marked in smaller arteries and a relation to involved segments could not always be made out. Lesions in arteries less than 400 microns in diameter and in arterioles were not conspicuous; one afferent arteriole in the kidney was found in which the entire wall was necrotic and structureless. Only near the hilum of the liver, where they were secondary to the arterial adventitial reaction, were veins involved.

The kidneys showed multiple small areas of infarction in various stages of organization; no recent

infarcts were seen. In the remarkably large amount of normal-appearing intervening renal parenchyma the only change aside from those in the arteries was a sprinkling of almost completely fibrosed glomeruli; this individual glomerular fibrosis could hardly be accounted for by the large artery involvement, so it probably represented either the residual of primary glomerular capillary involvement of polyarteritis nodosa as described by Davson et al.[2] or the sequela of the individual necrotizing renal arteriolitis noted above, which presumably was secondary to the hypertension.

In the heart there were only a few areas of interstitial lymphocytic infiltration, and no parenchymatous lesions were found in the liver, pancreas, intestines or adrenal glands. Presumably, the collateral circulation was adequate in all these situations.

The lungs showed much more microscopically than we had suspected on gross examination. In addition to congestion and edema there was an organizing pneumonia in sections taken from all lobes. The alveoli were packed with macrophages and fibrin, and there was intra-alveolar organization of fibrin by granulation tissue and a granulomatous reaction in the walls of the alveolar ducts, bronchioles and smaller bronchi. The pleura and some of the septums were thickened and edematous and showed areas of granulomatous inflammation. Except for a few small areas of acute bronchopneumonia, presumably terminal, no acute inflammation or necrosis was seen, and no eosinophils were found. No definite arterial lesions were found in the lungs.

Recent experience with the steroid treatment of polyarteritis nodosa has indicated that the steroid hormones may increase the tempo of the healing process of the arterial lesions, sometimes to the detriment of the patient. However, we have seen cases in this laboratory in the pre-steroid era,[4] and others are reported in the literature,[5] in which healing and healed lesions were found. In view of the short duration of the steroid therapy in this case it is unlikely to have been more than a secondary cause of the healing of the arterial lesions. Although it is generally considered that involvement of the lung in classic polyarteritis is unusual, lung lesions similar to those in this case have been described in polyarteritis nodosa.[6] The pulmonary lesion was demonstrable in the x-ray films before the nonprotein nitrogen rose, so uremia cannot be held responsible. We are forced to accept the lung lesion as resulting from the same process causing the generalized polyarteritis nodosa. Perhaps this is an expression of "focal allergic pneumonia" as suggested by Teilum,[7] although this would be somewhat at odds with the recent classification put forward by Zeek[8] that "necrotizing angiitis" can be differentiated into five groups, allergic granulomatous angiitis being separable from the more classic periarteritis nodosa.

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DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

REORGANIZATION Plan No. 1, of 1953, creating a department of health, education and welfare, was presented to Congress on March 12, and was approved by a special session of the House of Delegates of the American Medical Association in Washington two days later.

The seventy-nine-year-old campaign of the American Medical Association for such a department headed by a physician in the Cabinet has not borne fruit in the new plan. The secretary of the proposed department is not to be a physician, nor are the undersecretary or the two assistant secretaries. There is to be in the department a "special assistant" to the Secretary, who is to be a "recognized leader in the medical field" (the word "physician" is not used).

It may be surmised that if this plan had been presented by a hostile administration it would have been rejected by the spokesmen of the Association. This is not to say that the plan is bad; it has many virtues. But it is not all that was wanted. Half a loaf is better than a stone, and perhaps there is truth in the wry and cynical comment of Representative Judd, that in matters of practical politics there are times when one must rise above principle.

The practical politics of the situation lie in the fact that no complete reorganization of the outlook and policies of the Federal Security Administration as it stands is possible under the present rules of Civil Service. The legally entrenched employees of the Truman era cannot be discharged; it is necessary to let them and their organization wither while a new department takes over.

Just where medicine fits into this department remains to be demonstrated. At the moment complete and cheerful co-operation from the members of the profession is the happy watchword.

NEW DEAN AT TUFTS

TUFTS College Medical School marks its sixtieth year with the accession, this month, of a new dean, the ninth to assume administrative responsibility for the affairs of this New England institution. Dr. Joseph M. Hayman, Jr., the first dean to come to his duties from beyond the local area, succeeds Dr. Dwight O'Hara, who for more than sixteen years has been associated with the Dean's office (as vice-dean from 1937 to 1942, acting dean from 1942 to 1946 and dean since 1946). Dr. Hayman received his bachelor of arts degree at Haverford College in 1918, and his medical doctorate at the University of Pennsylvania School of Medicine in 1921. He served as intern in the Pennsylvania Hospital at Philadelphia and as assistant resident in the Thorndike Memorial Laboratory at the Boston City Hospital.

After filling the positions of instructor and assistant professor of pharmacology at the University of Pennsylvania, he went to Cleveland in 1929 as associate professor of medicine at Western Reserve

University School of Medicine, where he has been professor of medicine since 1949. He was also associate physician in the University Hospitals of Cleveland. Dr. Hayman will hold a professorship of medicine in addition to the office of dean at Tufts and an appointment as senior physician at the New England Center Hospital and at the Pratt Diagnostic Clinic.

During World War II he was chief of medicine in the Fourth General Hospital in the Southwest Pacific, consultant in medicine in the Southwest Pacific area and chief of medicine in the Moore General Hospital, Swannanoa, North Carolina, where he was awarded the Legion of Merit for his work. He is consultant to the Surgeon General of the United States Army and to the Veterans Administration.

Dr. Hayman is a member of the American Medical Association, Ohio State Medical Association, American Society for Clinical Investigation, Central Society for Clinical Research, American College of Physicians, Association of American Physicians, Society for Experimental Biology and Medicine, American Physiological Society and American Society for Pharmacology and Experimental Therapeutics. He is also a member of the Council on Pharmacy and Chemistry of the American Medical Association and of the Committee on Narcotics and Drug Addiction of the National Research Council. He was certified by the American Board of Internal Medicine in 1937.

In the contribution of more than 70 papers to the medical literature Dean Hayman has expressed his general interest in internal medicine and particular interest in renal physiology, kidney disease, heart failure and tropical medicine. The *Journal* welcomes him to New England and to his new position, confident that he will follow in the distinguished tradition of his predecessors.

GENERAL MEDICAL COUNCIL

Although communication is known to be highly developed in the birds and the bees, this faculty appears to have undergone atrophy of disuse in the portion of the human race concerned with problems of health. As Gregg* points out forcefully in an address to the medical deans, the total health program is severely handicapped by overspecialization and lack of intercommunication within the various health services and between them and the public. He points out that, "The medical care of the American people today is not the mere aggregate or sum of all the private practices of all the private practitioners of the country. It is complex and differentiated." It includes salaried physicians in schools, industry, public health and the military services, hospital administrators, medical teachers, nurses of all types, pharmacists, drug manufacturers, laboratory technicians, physical therapists and many others.

Dr. Gregg continues as follows:

> Can all these disparate groups, each deeply concerned with medical care, each closely related in purpose yet lacking in any medium of conference or form of exchange, effectively adjust American medicine to its changing matrix? We need in this country a general medical council representing the experience, the good will, the hopes and needs of many different groups now involved in medical care.

Such a council would serve a double purpose as a clearinghouse for information and opinion within its membership and as a channel of communication between the group and the lay public.

In Dr. Gregg's view the seriousness of the financial plight of the medical schools has never been adequately presented to the public. It is not generally realized that the present need of the medical schools amounts to only about 0.05 per cent of the national tobacco bill or about 0.02 per cent of the national liquor bill. Nor has the American public yet been made aware of the extent of the contributions that medical schools make to their communities.

The most obvious contribution is the direct medical service rendered to charity patients in teaching hospitals. If this is measured in dollars and cents according to the accepted rates of compensation of the Veterans Administration, its magnitude can be appreciated. In one Boston medical school, it is estimated that the charge for service rendered in accordance with this formula would amount to two and a half times its annual budget. And yet this is only one of the many community services rendered by a medical school that have gone unrecognized because unsung. Dr. Gregg's proposed council could not help promoting better understanding and co-

*Gregg, A. Communication and great medicine. *J. Med. Education* 28:17-21, 1953.

operation among the various members of the health team and might well become the trusted agency for the collation, interpretation and dissemination of unbiased health information to a public that is thirsting for it.

JOURNAL OF GERIATRICS

THE appearance, as of January, 1953, of Number 1 of the first volume of the *Journal of the American Geriatrics Society* throws into the discard a concept firmly fixed in the minds of many persons. For instead of an infant New Year driving from the scene a scythe-bearing, bald and bearded personification of Father Time, the parts are reversed; senescence has come into its own and youth, having had its fling, gives way to a rejuvenated octogenarianism.

The editor of the infant journal of old age states, quite accurately, that whereas life expectancy at birth has increased greatly since 1900, that at age sixty-five has increased only slightly. It is nevertheless quite obvious and might, indeed, be adopted as a geriatric slogan that a decrepit old gaffer of ninety-nine winters has a much better chance of surviving his hundredth birthday than has a healthy infant of but a single season.

Whatever may be the reasons for the rapid accumulation of an aged population — and it is estimated that by 1975 there will be between 17,000,000 and 20,000,000 people in this country sixty-five years of age and over — the obligation to try and make old age comfortable, serene and relatively useful is undeniable. The American Geriatrics Society was therefore established over ten years ago with the objective of "the clinical study of geriatric problems in the broadest sense, including the study of the causes, prevention and treatment of diseases of advancing years, the rehabilitation of patients and the dissemination of this knowledge."

And now, the Society, having grown from some 440 members in June, 1942, to a membership of 1500 in June, 1952, has achieved that degree of maturity marked by the sponsorship of its own monthly journal, dedicated to the proposition that old age should be made worth waiting for.

New York State Lunatic Asylum. — *This is a mammoth institution in its external appearance. In passing by, the traveller would be led to suppose the establishment was a fortress. Imperfection seems to be apparent even in this model lunatic asylum, as the managers state that ventilation was unprovided for in its original construction.*

Boston M. & S. J., *April 6, 1853*

CORRESPONDENCE

SUPRAVENTRICULAR TACHYCARDIA

To the Editor: It has been pointed out to me by Dr. H. M. Rogers that the article entitled "Supraventricular Tachycardia in the Fetus," which appeared in the December 11 issue of the *Journal*, by myself, Redding and Haubrich, overlooked still another case of probable nodal tachycardia in the fetus, reported in Dr. Rogers' paper, "Disturbances of Cardiac Rhythm and Conduction in Congenital Cardiac Disease: Report of 5 cases (*Ann. Int. Med.* 35:1276-1290, 1951). In March, 1948, the boy was eight years old and still subject to bouts of paroxysmal nodal tachycardia, not relieved by quinidine and not otherwise associated with heart disease. There are therefore at least 6 reported cases in the literature.

S. M. SANCETTA, M.D.

Cleveland, Ohio

RESEARCH IN HEART DISEASE

To the Editor: To a realist it appears that the actual prospects of research in heart disease are decidedly limited. Already, the control of infections and improved economic factors, together with the group of preventive and surgically curable extracardiac causes of heart disease, leave the largest proportion, comprising the arteriosclerotic, hypertensive and combined forms.

These are related to heredity: the first to physical degeneration or aging, and the second to overactivity or strain. They are as mysterious as life and death. They constitute the most difficult problem, one involving human eugenics.

GILBERT W. HAIGH, M.D.

Worcester, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Ambulatory Proctology. By Alfred J. Cantor, M.D., proctologist, Kew Gardens General Hospital, Long Island, New York. With a foreword by Beaumont S. Cornell, M.D., editor, *American Journal of Digestive Diseases.* Second edition, revised. 8", cloth, 563 pp., with 382 illustrations. New York: Paul B. Hoeber, Incorporated, 1952. $10.00.

The first edition of this special book was published in 1946. This new edition has been thoroughly revised and brought up to date. There are new chapters on antibiotics, diarrhea and electrosurgery, employing the thermal cutting unit. The technics of hemostasis and the new hemostatic agents, especially oxidized cellulose, are described in detail. Material on the postoperative management of proctologic surgery and on the physiology of immediate ambulation in its clinical application has been added. Lists of references are appended to the various chapters, and there is an index of subjects. The publishing is excellent. The book should be in all collections on the subject.

New and Nonofficial Remedies: Containing descriptions of the articles which stand accepted by the Council on Pharmacy and Chemistry of the American Medical Association on January 1, 1952: Issued under the direction and supervision of the Council on Pharmacy and Chemistry, American Medical Association. 12°, cloth, 838 pp. Philadelphia: J. B. Lippincott Company, 1952. $3.00.

This new volume in a standard reference series has been revised to include the articles and tests accepted by the Council on Pharmacy and Chemistry of the American Medical Association for the period ending January 1, 1952. The material is divided into three parts: accepted products; tests and standards for nonofficial products; and cumulative list and bibliography of unaccepted products. There is a good general index, and the publishing is excellent. The volume is recommended for all medical libraries.

Child Rorschach Responses: Developmental trends from two to ten years. By Louise B. Ames, Ph.D., director of research, Gesell Institute of Child Development, and member of the Society for Projective Techniques and the Rorschach Institute, Incorporated; Janet Learned, M.A., director of Preschool Service; Ruth W. Métraux, M.A., speech and Rorschach specialist; and Richard N. Walker, M.A., research assistant. 8°, cloth, 310 pp., with 39 tables. New York: Paul B. Hoeber, Incorporated, 1952. $7.50.

The authors of this book are all connected with the Gesell Institute of Child Development. They present the findings on 650 children from two to ten years of age. Comparisons are made at each age level with the developmental patterns reported in earlier works by the Gesell group. The material is presented in two parts: general considerations, and the analysis of the age groups from two to ten years of age. The ages from two to five years are given in half years. The final chapters are devoted to normal expectancies of an adult Rorschach record, clinical applications and a summary. There is a bibliography of 89 references and a good index. The publishing is excellent.

Annual Review of Medicine. Vol. 3. Windsor C. Cutting, editor, Stanford University School of Medicine, and Henry W. Newman, associate editor, Stanford University School of Medicine. 8°, cloth, 442 pp. Stanford, California: Annual Reviews, Incorporated, 1952. $7.50.

This volume of a standard reference series presents 17 articles by specialists in their various fields on subjects in medicine, including psychiatry, radiology and radioactivity, toxicology and neoplastic diseases. The final chapter is devoted to an annotated list of reviews in medicine. Extensive bibliographies are appended to the various chapters, and there are comprehensive indexes of authors and subjects. The publishing is good. The volume reminds one of the well known German *Ergebnisse*. The series should be in all medical libraries.

Nuclear Science Abstracts. Vol. 6, No. 12A, Abstracts 3481-3733, June 30, 1952. By the United States Atomic Energy Commission. 4°, paper, 27 pp. Oak Ridge, Tennessee: Technical Information Service, 1952. 25¢.

This periodical, now in its sixth year, is devoted to literature on nuclear science, and is divided into seven sections: general considerations, biology and medicine, chemistry, engineering, mineralogy, metallurgy and ceramics, and physics. It is valuable for general reference purposes.

International Sanitary Regulations: Proceedings of the Special Committee and of the Fourth World Health Assembly on WHO Regulations No. 2. 4°, paper, 443 pp. Geneva, Switzerland: World Health Organization, 1952. 16/3, $2.25, Sw. fr. 9. (Official records of the World Health Organization No. 37.)

This volume is divided into two parts. The first is devoted to the minutes of the thirty-six meetings of the special committee, the subcommittee on the Mecca pilgrimage and the Committee on International Sanitary Regulations. The second part contains the international sanitary regulations, a table of comparisons and an index to the regulations. There is a comprehensive general index, and the publishing is excellent. This important document should be in all collections on public health.

Textbook of Medicine. By various authors. Edited by Sir John Conybeare, K.B.E., M.C., D.M. (Oxon.), F.R.C.P., physician to Guy's Hospital, London; and W. N. Mann, M.D. (Lond.), F.R.C.P., assistant physician to Guy's Hospital, London. Tenth edition. 8°, cloth, 912 pp., with 31 illustrations and 31 X-ray plates. Baltimore: Williams and Wilkins Company, 1952. $8.00.

This standard textbook of medicine was first published in 1929 and since then has gone through ten editions and sixteen printings. The previous edition was published in 1947. The book is the joint work of 17 contributors. This new edition has been revised, and brought up to date by the incorporation of new material. An appendix on the sulfonamide and antibiotic drugs has been added. This is a practical book, written without reference to the literature on the various subjects. The printing was done in Great Britain. The publishing is excellent, with one exception: valuable tables should not be placed on the inside of the covers, where they are apt to be defaced.

Physical Medicine in General Practice. With twenty-two contributors. Edited by William Bierman, M.D., and Sidney Licht, M.D. Third edition. 8°, cloth, 798 pp., with 234 illustrations. New York: Paul B. Hoeber, Incorporated, 1952. $12.50.

This new edition of a standard book has been revised, and the material brought up to date, actually constituting a new book. Chapters on functional muscle testing, microwave therapy, neuromuscular re-education, ultrasound and care of the amputee have been added. Medical rehabilitation has also been included. The work is the joint effort of 22 authors, 3 of whom are from Boston: Drs. Sidney Licht, Thomas L. DeLorme and Vernon S. Dick. Bibliographies are appended to the chapters, and there is an extensive and valuable index. The publishing is excellent, and the book should be in all collections on the subject.

Symposium on Radiobiology: The basic aspects of radiation effects on living systems. Oberlin College, June 14-18, 1950. Edited by James J. Nickson. New York: John Wiley and Sons, Incorporated, 1952. $7.50. (Sponsored by the National Research Council of the National Academy of Sciences.)

This volume includes the papers, 23 in number, and discussions, presented at the Oberlin symposium. Lists of references are appended to the chapters. There is a table of contents, but unfortunately an index has been omitted. The publishing is excellent. The book is an important reference tool and should be in all collections on the subject.

The "Neurility" of the Kidney: A monograph on nerve supply to the kidney. By C. G. de Muylder, M.D. 4°, cloth, 80 pp., with 46 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $5.00.

This monograph summarizes the results of fourteen years' study of the nerve supply to the kidney. Renal innervation is discussed in its normal and pathologic aspects. The final chapter deals with nephrosclerosis and neoplastic processes in the kidney and neurogenesis. The pertinent literature is reviewed, and there is a bibliography of 212 items. The printing was done in Holland. The illustrations are excellent.

Normal Blood Pressure and Hypertension: New definitions. By Arthur M. Master, M.D., cardiologist, Mount Sinai Hospital, New York City, and associate clinical professor of medicine, Columbia University College of Physicians and Surgeons; Charles I. Garfield, M.D., research assistant in cardiology, Mount Sinai Hospital, New York City; and Max B. Walters, M.D., F.R.C. (Can.), member, Heart Station, Vancouver General Hospital, Canada. 8°, cloth, 144 pp., with 36 illustrations. Philadelphia: Lea and Febiger, 1952. $4.00.

For a number of years the authors conducted an investigation on the true normal limits of the blood pressure. They studied 74,000 unselected patients, and a summary of the results is presented in this monograph. They believe that the common concept of the normal level as 150 systolic, 90 or 95 diastolic, is unsound, and present new limits, with explanations in detail. The monograph should be in all collections on the subject.

Spleen Puncture. By Sven Moeschlin, lecturer, University Medical Clinic, Zürich. Translated by A. Piney, M.D. 8°, cloth, 229 pp., with 55 illustrations and 32 tables. New York: Grune and Stratton, 1951. $5.50.

The book by Moeschlin was first published in Switzerland in 1947. Advantage has been taken of this English translation to add new material and 40 illustrations, and the section on recent literature has been reviewed. The material is based on the personal performance of over 300 splenic punctures for diagnostic purposes, made between 1939 and 1949. The text is divided into two parts: general and special. The general part discusses the approved technic and the different types of cells. The special part has to do with the various diseases to which the method is applicable. The literature on the procedure is thoroughly reviewed, and there is a bibliography of 12 pages. The printing was done in England, and the publishing is excellent. The book is recommended to all medical libraries and to all physicians interested in the subject.

The Knee and Related Structures: Injuries, deformities, diseases, disabilities. By Philip Lewin, M.D., F.I.C.S., professor and chairman of the Department of Bone and Joint Surgery, Northwestern University Medical School, attending orthopedic surgeon, Cook County Hospital, senior attending orthopedic surgeon, Michael Reese Hospital, and professor of orthopedic surgery, Cook County Graduate School of Medicine, Chicago. 8°, cloth, 914 pp., with 333 illustrations and 2 colored plates. Philadelphia: Lea and Febiger, 1952. $16.00.

Dr. Lewin is well known for his books on the ankle and on the back. This new book on the knee joint and its ligaments, and the patella, is comprehensive in scope, beginning with anatomy and ending with tumors. There are chapters on the metabolic and endocrine disorders affecting the knee, and on equalization of the length of the lower extremities. An appendix discusses a number of related subjects, including the surgical approaches to the knee, injuries in mountain troops, ruptures of the muscles and tendons of the calf of the leg, and a list of 133 "genugrams," short axioms dealing with the knee. There is a comprehensive bibliography of 28 pages and a good index. The publishing is excellent. The book should be in all medical libraries and in the private libraries of orthopedic surgeons.

Manual of Electrocardiography. By Benjamin F. Smith, M.D., professor of clinical medicine, Baylor University College of Medicine, member of active staff and chief of electrocardiographic laboratory, St. Joseph's Infirmary, consultant in cardiology, Veterans Administration Hospital, consultant in medicine, Hermann Hospital, and senior associate physician, Jefferson Davis Hospital, Houston, Texas. 8°, cloth, 215 pp., with 119 illustrations. Houston: Elsevier Press, Incorporated, 1952. $4.50.

This manual has been used for a number of years in the instruction of students at the College of Medicine of Baylor University. It has now been revised for publication. It presents the basic principles of electrocardiography and discusses the most recent developments. There is a good index, and the publishing is excellent.

Gastrointestinal X-Ray Diagnosis. By Max Ritvo, M.D., assistant professor of radiology, Harvard Medical School, instructor in biology, Tufts Medical School, director, Department of Radiology, Boston City Hospital, and associate in radiology, Beth Israel Hospital, Boston; and I. A. Shauffer, M.D., instructor in radiology, Harvard Medical School, instructor in radiology, Tufts Medical School, and visiting radiologist, Boston City Hospital. 8°, cloth, 838 pp., with 470 illustrations. Philadelphia: Lea and Febiger, 1952. $20.00.

The authors describe and discuss the various lesions of the gastrointestinal tract that can be diagnosed by x-ray examination. The material is arranged on an anatomic basis. The first chapter, which deals with general considerations, is followed by chapters on the pharynx and esophagus, stomach, the intestines, the appendix, gall bladder and liver, the pancreas, spleen, mesentery, omentum, peritoneum and abdomen, and hernia (diaphragmatic and rare forms). Lists of references are appended to the chapters, and there is a good index. The publishing is excellent. The book is recommended for all medical libraries, and to radiologists and gastroenterologists.

Marriage, Morals and Medical Ethics. By Frederick L. Good, M.D., LL.D., and Reverend Otis F. Kelly, M.D. 8°, cloth, 202 pp. New York: P. J. Kenedy and Sons, 1951. $3.50.

The authors have presented a clarification of the Catholic position in present-day medicomoral problems. The subjects discussed include the Christian concepts of matrimony, principles of morality, sexual constitution, normal conception, pregnancy and labor, complications of pregnancy and regulation of conception. There are chapters on psychiatry, ecclesiastical matrimonial court procedure, and baptism and extreme unction. An introduction has been written by the Most Rev. Richard J. Cushing, D.D., Archbishop of Boston. The book bears his official imprimatur and the official approval of the Rev. Timothy P. O'Connell, D.D., censor of the diocese.

Malaria: Basic principles briefly stated. By Paul F. Russell, M.D., M.P.H., division of medicine and public health, Rockefeller Foundation, and consultant to the Surgeon General, United States Army. 8°, cloth, 210 pp., with 64 illustrations. Oxford, England: Blackwell Scientific Publications, 1952. $7.75. (Distributed by Charles C Thomas, Springfield, Illinois; Publication No. 126, *American Lecture Series.*)

This monograph endeavors to present the principles of malariology in a brief form. The material is divided into a number of chapters, including the plasmodia, pathology, clinical course and therapy, anophelines, epidemiology and prevention and control. There is a bibliography of 13 pages, and author and subject indexes. The illustrations, including the color plates, are excellent. The small book should be in all collections on malaria.

NONCLINICAL NOTES

CHAIRMAN OF HEALTH COUNCIL

Dr. Henry J. Bakst, professor of preventive medicine at Boston University School of Medicine and director of home medical service and outpatient service, Massachusetts Memorial Hospitals, has been elected chairman of the Health Council of United Community Services of Greater Boston for a three-year term.

Dr. Bakst succeeds Dr. George C. Shattuck, who has served as chairman of the Health Council and its predecessor, the Boston Health League, for thirty years.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the third-floor amphitheater of the Boston Psychopathic Hospital, 74 Fenwood Road, on Tuesday, April 14, at 8:15 p.m. The following program will be presented by the Department of Psychiatry, Boston Psychopathic Hospital, Dr. Harry C. Solomon presiding:

Psychotherapy in the Psychoses (thirty minutes). Elvin V. Semrad, M.D., Shepard Ginandes, M.D. and Donald Gair, M. D.

Psychosurgery in the Psychoses — Presentation of Cases (thirty minutes); Discussion of Types of Surgical Approach, Indications and Long-Term Results (thirty minutes). Harry C. Solomon, M.D., Milton Greenblatt, M. D., J. Sanbourne Bockoven, M.D., Robert W. Hyde, M.D., Paul Barrabee, Ph.D., and Dan Funkenstein, M. D.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

The annual meeting of the Middlesex South District Medical Society will be held at the Hotel Continental, Cambridge, on Wednesday, April 22.

Program

11:15 a.m. Business meeting (reading of *Minutes*, Treasurer's report, election of officers and unfinished business — remarks by the President and reports of committees, as well as new business and communications and reading of obituaries).

12 m. Annual Oration. "Pernicious Anemia — a Continued Story." Dr. William B. Castle, professor of medicine, Harvard Medical School, director of the Thorndike Memorial Laboratory and Director of the Second and Fourth Medical Services, Boston City Hospital. (Dr. Castle was awarded the Major General Leonard Wood Medal by the Boston City Hospital Alumni Association on April 30, 1949, "in recognition of contributions to medicine and humanity," as a result of his work in pernicious anemia.)

1 p.m. Luncheon.

PHI DELTA EPSILON LECTURE

The annual Phi Delta Epsilon Lecture will be given at University of Vermont College of Medicine, Burlington, on April 17. Dr. Homer W. Smith, professor of physiology, New York University-Bellevue Medical Center, will speak on the subject "The Development of Modern Renal Physiology."

SOCIETY MEETINGS AND CONFERENCES

April 2-27. Consultation Clinics for Crippled Children in Massachusetts. Page 523, issue of March 19.

April 9. Pentucket Association of Physicians. Haverhill. 8:30 p.m.

April 10. New England Society of Anesthesiologists. Page 395, issue of February 26.

April 10-12. American Association of the History of Medicine. Page 308, issue of February 12.

April 13-May 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

April 14. Harvard Medical Society. Page 619.

April 14. New York Society for Circulatory Diseases and New York Cardiological Society. Page 526, issue of March 19.

April 15. Tufts Medical Alumni Association. Page 525, issue of March 19.

April 15. Massachusetts Academy of General Practice. Page 480, issue of March 12.

April 16-18. Postgraduate Course in Obstetrics and Pediatrics. Page 525, issue of March 19.

April 17. Phi Delta Epsilon Lecture. Notice above.

April 19-24. National Industrial Health Conference. Page 308, issue of February 12.

April 20. Hartford Medical Society. Page 42, issue of January 1.

April 20-22. American Academy of Pediatrics. Hotel Statler, Boston.

April 21. South End Medical Club. Page 570, issue of March 26.

April 22. Middlesex South District Medical Society. Notice above.

April 24-29. American College of Allergists. Page 570, issue of March 26.

April 25. Boston City Hospital Alumni Association. Page 570, issue of March 26.

April 25. Alumni Association of the State University College of Medicine at New York City. Page 396, issue of February 26.

April 25. Graduate Club of Boston. Phi Delta Epsilon Medical Fraternity. Page 307, issue of February 12.

April 29 and October 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

May 2. When is the Treatment of Mitral Stenosis Surgical? Drs. Laurence B. Ellis and Dwight E. Harken. Mount Auburn Hospital, Cambridge. 10:05 a.m.

May 7-9. American Goiter Association. Page 480, issue of March 12.

May 11-13. Aero Medical Association. Page 526, issue of March 19.

May 19-21. Massachusetts Medical Society. Hotel Statler, Boston.

May 25-31. First World Congress on Fertility and Sterility. Page 1001, issue of December 18.

May 30 and 31. Society for Investigative Dermatology, Inc. Page 570, issue of March 26.

June 7-9. American College of Cardiology. Page 395, issue of February 26.

June 28-July 2. American Society of X-Ray Technicians. Page 480, issue of March 12.

District Medical Societies

ESSEX NORTH

May 13. Andover Country Club, Shawsheen.

MIDDLESEX SOUTH

April 22. Hotel Continental, Cambridge.

WORCESTER

May 6. Annual Meeting. Sheraton Hotel. Dr. Louis H. Bauer, President, American Medical Association.

Calendar of Boston District for the Week Beginning Thursday, April 9

Thursday, April 9

*8:30-10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
9:00-10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.-12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.-12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
5:00 p.m. Case Presentation and Pathological Discussion followed by a Subject of Special Presentation. Joslin Amphitheater, New England Deaconess Hospital.
*5:00-6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

Friday, April 10

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.-1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:30-11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
12:00 m.-1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
1:30-9:00 p.m. New England Society of Anesthesiologists. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00-10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

Saturday, April 11

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.-12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

Monday, April 13

8:00-9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgical Cases. New England Deaconess Hospital.
*8:30-9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:15-1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00-3:30 p.m. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.
*7:00-9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

Tuesday, April 14

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.-12:00 m. Regular Grand Rounds of the Pediatric Department. Dowling Amphitheater, Boston City Hospital.
*12:00 m.-1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15-1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00-6:30 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
8:15 p.m. Harvard Medical Society. Boston Psychopathic Hospital, 74 Fenwood Road.

Wednesday, April 15

10:00 a.m.-7:00 p.m. (Followed by dinner and speaker.) Massachusetts Academy of General Practice. Morning Session. Lower Out-Patient Amphitheater, Massachusetts General Hospital. Afternoon meeting sessions. Hotel Shelton, 91 Bay State Road.
*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.-1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
12:30-1:30 p.m. Weekly Staff Review of Autopsies. Dr. William J. Meissner. Joslin Auditorium, New England Deaconess Hospital.
4:00 p.m. Tufts Medical Alumni Association. Open House at the Medical School.
*5:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00-5:30 p.m. Fracture Lecture. Boston City Hospital.
6:30 p.m. Tufts Medical Alumni Association. Annual Dinner Meeting. Somerset Hotel, Boston.
7:30 p.m. Lahey Clinic Lecture. Endocrinology. Drs. Lewis M. Hurxthal and A. Seymour Parker, Jr. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.